| REVIEW ARTICLE |

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Lactate and pyruvate concentrations and their ratios as a marker for local or systemic hypoxic-ischaemic injury

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Abstract

Lactate and pyruvate play a crucial role in assessing the metabolic status of critically ill patients. Under normal conditions, lactate is produced by anaerobic glycolysis and is excreted by the liver and kidneys. Elevated lactate levels, referred to as hyperlactatemia, can be caused by various conditions, including tissue hypoxia, impaired oxygen utilisation, and metabolic disorders. Hyperlactatemia is often associated with adverse outcomes, particularly in critical illnesses such as sepsis and shock. Lactic acidosis, characterised by both elevated lactate levels and decreased blood pH, further exacerbates metabolic acidosis and leads to multi-organ failure if left untreated. The lactate-to-pyruvate ratio (L/P) is a potential biomarker to differentiate between hypoxic and non-hypoxic hyperlactatemia. A high L/P ratio indicates significant mitochondrial dysfunction and impaired oxidative metabolism, which often means a poorer prognosis. Conversely, a lower L/P ratio tends to indicate a more favourable outcome. However, the clinical utility of the L/P ratio is limited by the difficulty of measuring pyruvate and its dependence on factors such as pH and redox potential. Although lactate measurements are routinely performed in the emergency department and intensive care unit, there is little data on the prognostic value of the L/P ratio. Recent studies have shown that persistent hyperlactatemia with an elevated L/P ratio during the first 24 hours of septic shock correlates with increased mortality and organ failure. In addition, research on critical conditions such as the coronavirus 2019 disease (COVID-19) suggests that circulating pyruvate levels may also predict disease severity. Overall, the L/P ratio has the potential to be a valuable tool for monitoring critically ill patients, but further research is needed to confirm its broader clinical applicability.

Key words: ***lactate; pyruvate; lactate-to-pyruvate ratio; hyperlactatemia; critical illness; prognosis***.

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Introduction

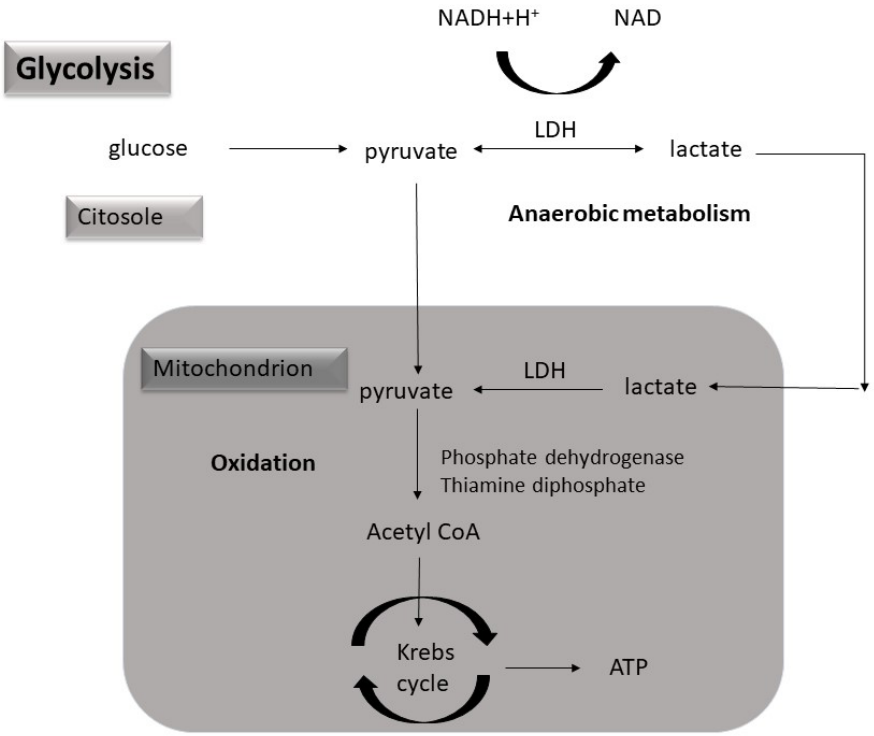
The proper functioning and integrity of all cells depends on an adequate supply of oxygen. Severe acute illnesses are often associated with poor tissue perfusion and/or reduced oxygen levels in the blood (hypoxemia), which can lead to tissue hypoxia. Tissue hypoxia is a serious complication in critical patients and, if unresolved, can lead to multi-organ failure and death (Higgins, 2017). Research by Ferguson et al. (2018) suggests that there is a common misconception that lactate is a toxic waste product of hypoxia and/or hypoperfusion. Traditionally, blood lactate concentration has been used as a marker for monitoring tissue oxygenation. The measurement of lactate in patients began in the 20th century, when it was discovered that the accumulation of lactic acid was responsible for metabolic acidosis in patients with reduced blood flow and shock. Later, Huckabee (1961) documented cases of hospitalised patients with remarkable lactate accumulation and acid-base abnormalities. Today, lactate measurement is crucial in emergency and intensive care patients, and the technology for measuring lactate has evolved significantly. Modern, advanced portable devices now allow lactate measurement by non-laboratory personnel, with results available within one to two minutes, contributing to faster initiation of treatment.

Metabolism of lactate and pyruvate

Lactate is produced by various tissues in the human body, with the highest production rate in the skeletal muscles. Under physiological conditions, lactate is efficiently excreted by the liver, with the kidneys making a minor contribution to its removal (Connor et al., 1982; Consoli et al., 1990). Lactate is a by-product of glucose metabolism, in particular the end product of anaerobic glycolysis. Glycolysis is the metabolic pathway in which glucose is broken down to pyruvate, resulting in a net gain of two adenosine triphosphate (ATP) molecules. This process takes place in the cytoplasm and involves a series of enzyme-catalysed reactions (Gladden, 2004). In the presence of oxygen (aerobic conditions), pyruvate enters the mitochondria where it is converted to acetyl coenzyme A (acetyl-CoA) by the enzyme pyruvate dehydrogenase. Acetyl-CoA then enters the citric acid cycle and contributes to oxidative phosphorylation and further ATP production (Brooks, 2009) (Figure 1).

Under anaerobic conditions or when oxidative metabolism is impaired, pyruvate is reduced to lactate by the enzyme lactate dehydrogenase (LDH). This process regenerates nicotinamide adenine dinucleotide (NAD+), which is required for the continuation of glycolysis (Gladden, 2004). The accumulation of lactate can lead to lactic acidosis,

Figure 1. Schematic representation of lactate and pyruvate metabolism in glycolysis. Modified from Ryoo and Kim, 2018



especially in cases of tissue hypoxia or mitochondrial dysfunction. The lactate-to-pyruvate (L/P) ratio is a useful marker to distinguish between different types of hyperlactatemia and helps to assess whether the condition is due to impaired oxygen utilisation or other metabolic disturbances (Halestrap, 2013).

Lactate plays an important role in metabolism and skeletal muscles function in small animals. During intense exercise, anaerobic glycolysis leads to lactate accumulation in muscle fibres, affecting muscle function and adaptation (Kyun et al., 2021). Furthermore, lactate accumulation in animals is not only a consequence of exercise; various pathological conditions can lead to elevated lactate levels, indicating underlying health problems. Monitoring lactate levels in animals provides valuable insight into the severity and prognosis of disease, aiding in the diagnosis and treatment of various pathological conditions.

L-lactate and D-lactate

Lactate occurs in two stereoisomeric forms: L-lactate and D-lactate. Current lactate measurements mainly cover L-lactate, the predominant isomer formed in humans. D-lactate is primarily formed by bacterial fermentation in the large intestine, especially in the presence of large quantities of unabsorbed carbohydrates. Under conditions characterised by an altered gut microbiota and high carbohydrate intake (e.g., short bowel syndrome), there is increased production of D-lactate, which can enter the systemic circulation and potentially lead to neurological symptoms (Petersen, 2005). D-lactate is thought to be converted to pyruvate in the liver by the enzyme D-2-hydroxy acid dehydrogenase, although this process is much slower compared to the metabolism of L-lactate by L-lactate dehydrogenase (L-LDH) (Tubbs, 1965).

Hyperlactatemia and lactic acidosis

The normal values for lactate in healthy tissue are below 2 mmol/L, and an increase in lactate co ncentration is referred to as hyperlactatemia. The combination of hyperlactatemia and acidosis, where the blood pH is <7.35, is defined as lactic acidosis (Suetrong and Walley, 2016), which in turn can cause metabolic acidosis (Sacks, 2006). Hyperlactatemia occurs when the rate of lactate release from peripheral tissues into the bloodstream exceeds the rate of lactate clearance by the liver and kidneys. Both increased lactate production and impaired lactate clearance/metabolism can contribute to its development. Since oxygen is critical for pyruvate oxidation, any condition that deprives tissues of oxygen can lead to increased lactate production, which then accumulates in the bloodstream at a rate that exceeds clearance by the liver and kidneys. This problem is exacerbated by acidosis, as the liver's ability to remove lactate from the bloodstream is pH-dependent and is significantly impaired at a lower blood pH. Experimental data suggest that at a blood pH of 7.0 or less, lactate uptake is so severely impaired that the liver produces more lactate than it removes (Lloyd et al., 1973).

Hyperlactatemia is categorized into two main types: Type A and Type B, as originally proposed by Woods and Cohen (1976). Type A lactic acidosis is primarily associated with tissue hypoxia resulting from impaired perfusion, commonly seen in haemorrhagic, cardiogenic, or septic shock. These conditions often arise from trauma, surgical interventions, or acute critical illness. Although traditionally attributed to hypoxia, recent evidence suggests that lactic acidosis in septic states may occur even with preserved perfusion, highlighting the importance of both oxygen delivery and blood oxygen content in maintaining adequate tissue oxygenation (Higgins, 2017). Furthermore, Type A lactic acidosis may develop in response to acute increases in muscle activity, such as during seizures or strenuous exercise (Orringer et al., 1977), and under conditions such as severe anaemia (Essex et al., 1998), hypoxemia (Aberman and Hew, 1978), or carbon monoxide poisoning (Foster et al., 1999). In contrast, Type B lactic acidosis occurs despite adequate tissue perfusion and oxygenation. It is typically linked to impaired lactate metabolism, with the liver and kidneys playing key roles in lactate clearance through the citric acid cycle and gluconeogenesis. Consequently, liver or renal dysfunction, regardless of aetiology, increases the risk of developing hyperlactatemia and, in rare cases, Type B lactic acidosis. Haematology malignancies such as leukaemia and lymphoma are frequently associated with this form (Aberman and Hew, 1978). Type B lactic acidosis is further subdivided into three categories: B1, associated with reduced lactate clearance (e.g., hepatic insufficiency); B2, linked to drug or toxin exposure; and B3, related to inborn errors of metabolism (Woods and Cohen, 1976). Among these, B2 is the most common and includes agents such as metformin, ethanol, cyanide, and others. Metformin-induced lactic acidosis, in particular, is often observed in patients with underlying hepatic or renal dysfunction (Stacpoole, 1998). Subtype B3 encompasses rare congenital metabolic disorders characterised by enzyme deficiencies, including pyruvate dehydrogenase, pyruvate carboxylase, fructose-1,6-diphosphatase, and glucose-6-phosphate dehydrogenase deficiencies (Farrell et al., 1975; Rallison et al., 1979).

In summary, understanding the underlying pathophysiology and classification of hyperlactate-

mia is essential for accurate diagnosis and effective management, particularly in critically ill patients where elevated lactate levels may have multiple aetiologies.

The lactate/pyruvate ratio

The proposed method for distinguishing hypoxic hyperlactatemia from hyperlactatemia due to increased glycolytic flux involves measuring the lactate/pyruvate (L/P) ratio. The L/P ratio reflects the cytosolic redox potential and the balance between anaerobic and aerobic metabolism in the body. A higher L/P ratio indicates a significant impairment of oxidative metabolism typically associated with mitochondrial dysfunction. Conversely, under non-hypoxic conditions, an increase in lactate levels may occur without a corresponding increase in the L/P ratio. This phenomenon is relatively rare as the use of the L/P ratio is limited; redox potential can be influenced by factors other than oxygen utilisation (Levy, 2006). The measurement of pyruvate is complex and is not usually performed in routine clinical practice. Pyruvate tends to degrade rapidly, which can lead to falsely elevated L/P ratios (Hotchkiss and Karl, 1992). The L/P ratio is also pH-dependent, where a drop in the pH value by 0.3 units can lead to a doubling of the ratio. An L/P ratio of more than 30 can be achieved by changing the pH alone. Therefore, the L/P ratio is particularly useful when hyperlactatemia persists after pH normalisation, as it helps to differentiate hypovolemia with secondary hypoxia from other underlying causes (Leverve, 1999). However, the L/P ratio should be interpreted with caution, as its primary utility is in predicting outcomes. Persistent hyperlactatemia and an elevated L/P ratio within the first 24 hours of septic shock are associated with a higher risk of multiorgan failure and mortality, underscoring the importance of anaerobic metabolism and tissue hypoxia in the perioperative deterioration of critically ill patients. Furthermore, this could be due to impaired lactate clearance due to hepatic hypoperfusion and hepatocellular dysfunction, resulting in impaired lactate and pyruvate metabolism, which correlates with the severity of shock and multiorgan failure (Bakker et al., 1996). Conversely, hyperlactatemia with a lower L/P ratio is generally indicative of a more favourable prognosis (Redant et al., 2019).

Acid base status

Maintaining the acid-base balance is essential for physiological homeostasis, with blood pH normally ranging between 7.35 and 7.45. This balance is regulated by the bicarbonate buffer system and maintained by the kidneys and lungs. Disruptions can lead to acidosis or alkalosis, both of which affect cellular function and enzyme activity. Lactate, a byproduct of anaerobic metabolism, plays a central role in metabolic acidosis. As lactate dissociates into hydrogen ions (H+) and lactate ions, it contributes directly to the drop in pH and the development of acidosis (Gladden, 2004).

In critically ill patients, especially those with sepsis or shock, persistent hyperlactatemia and acidosis can indicate poor tissue perfusion and predict an unfavourable outcome (Li et al., 2022). Lactic acidosis, a specific form of metabolic acidosis, reflects both an increase in acid load and a reduced buffering capacity, which further exacerbates the acid-base imbalance (Halestrap, 2013).

Measurement and sampling

Various devices are available for lactate measurement, including portable point-of-care analysers and larger desktop devices for blood gas and acid-base analysis (Drobatz et al., 2018). Although some guidelines advocate the use of arterial blood for lactate measurement, venous blood is an acceptable alternative as the results do not show clinically significant differences (Lavery et al., 2000). The most commonly used method for lactate analysis is amperometry, in which a lactate-sensitive electrode is coated with lactate oxidase. This enzyme catalyses the conversion of lactate to pyruvate and hydrogen peroxide, with the hydrogen peroxide subsequently quantified by amperometric measurement (Fine-Goulden and Durward, 2014). Since hyperlactatemia can occur with or without a concomitant acid-base imbalance, concomitant acid-base parameters are important to assess the clinical significance and underlying cause of hyperlactatemia. Therefore, lactate measurement is optimally performed in conjunction with a comprehensive acid-base and electrolyte panel (Hopper and Epstein, 2013). In many cases, lactate is measured immediately in emergency and critical patients. *In vitro* glycolysis and subsequent lactate production continue after blood collection, resulting in a 30% increase in lactate concentration within 30 minutes if the sample is stored at room temperature. Therefore, blood samples should be analysed immediately after collection (Wennecke, 2004). Samples that cannot be analysed immediately should be stored on ice in the appropriate collection tube for the analyser, and preferably analysed within 60 minutes of collection (Noordally and Vincent, 1999). Particular care should be taken when collecting blood samples from catheters infusing lactate-containing fluids, as there is a possibility that lactate levels may be falsely elevated (Jackson et al., 1997).

There are few analytical techniques for pyruvate measurement. Accurate quantification of pyruvate in clinical laboratories is essential for

diagnosing metabolic and mitochondrial disorders. Several analytical methods have been developed, each offering unique advantages in terms of sensitivity, sample volume, and clinical applicability (Wulkan et al., 2001). Spectrophotometry is another established method, based on the enzymatic conversion of pyruvate to lactate by lactate dehydrogenase (Landon et al., 1962). Capillary electrophoresis with conductivity detection has emerged as a useful method in reproductive medicine (Alimagham et al., 2015). A limitation of pyruvate measurement is that it is difficult to perform routinely, as samples must be immediately stored on ice and deproteinised (Magnoni et al., 2003).

Lactate and pyruvate in clinical settings

An increase in lactate levels can have a variety of causes, and its clinical significance depends on the underlying aetiology. This emphasises the importance of considering all possible causes in the initial assessment and interpreting lactate levels in the context of the overall clinical picture. As multiple factors can contribute to an increase in lactate levels in an individual patient, interpretation can be difficult, and lactate should not be used as a specific marker for diagnosis or prognosis without carefully considering the overall clinical context (Andersen et al., 2013). Relying solely on lactate as a marker of anaerobic metabolism can be misleading. To accurately assess anaerobic metabolism, pyruvate levels should also be measured, as pyruvate is converted to lactate by lactate dehydrogenase under anaerobic conditions. The L/P ratio provides a more accurate indication of the balance between aerobic and anaerobic metabolism, as it reflects the cytosolic ratio of reduced to oxidized NAD+. Therefore, the L/P ratio is a more reliable indicator of cellular energy status. The disadvantage of pyruvate measurement is that it can be difficult to perform routinely, as samples must be immediately placed on ice and deproteinised (Magnoni et al., 2003). Rimachi et al. (2012) found that 77% of patients had hyperlactatemia at the onset of shock, decreasing to 56% after 12 hours and 40% after 24 hours. Of these hyperlactatemia episodes, 73% were associated with an increased L/P ratio at the onset of shock. This association remained stable for 8 hours but decreased to 50% by 24 hours. The progression of lactate and L/P ratios varied between survivors and non-survivors, with survivors exhibiting rapid declines, whereas non-survivors maintained consistently high levels. Lactate and L/P levels were higher in patients who died within 24 hours of shock, although the difference was not statistically significant compared to patients who died later in intensive care. Zoremba et al. (2014) also investigated lactate and L/P ratio in rat muscle before, during, and at recovery from global hypoxia. Their results pointed out that before hypoxia, basal muscular lactate levels remained stable. Upon the onset of hypoxia, extracellular lactate rapidly increased, peaking immediately after the 30-minute hypoxic period. During reoxygenation with air, lactate levels returned to baseline within 40 minutes. In the control group, lactate remained stable throughout the entire period.

Animals subjected to hypoxia showed a significant increase in the L/P ratio, which normalised during reoxygenation, returning to baseline within 30 minutes and remaining stable thereafter. In clinical practice, the tissue-specific L/P ratio may serve as a reliable biomarker for assessing the metabolic status of critically ill patients (Klaus et al., 2003). Multiple studies have shown that elevated lactate levels upon admission and sustained hyperlactatemia are correlated with an unfavourable outcome (Trzeciak et al., 2007; Soliman and Vincent, 2010). However, there is limited data regarding the prognostic significance of the L/P ratio (Weil and Afifi, 1970). During the COVID-19 crisis, pyruvate was studied in critical COVID-19 patients. One study pointed out that body mass index and circulating levels of creatinine, D-dimer, and pyruvate were the main determinants of COVID-19 severity. To further confirm their findings, they conducted a classification and regression tree analysis that confirmed that circulating pyruvate was the strongest predictor of COVID-19 severity (Ceperuelo-Mallafrė et al., 2022).

Conclusion

The lactate-to-pyruvate (L/P) ratio provides valuable insight into the metabolic status of critically ill patients and is a potential marker for differentiating between hypoxic and non-hypoxic hyperlactatemia. Elevated lactate levels associated with a high L/P ratio are associated with a poor outcome, including multiorgan failure and mortality. Although lactate measurement is widely used in clinical practice, the prognostic significance of the L/P ratio has not been adequately studied due to difficulties with pyruvate measurement and the sensitivity of the ratio to pH and redox status. Recent studies, including those on COVID-19 patients, suggest that the L/P ratio may have additional prognostic value, particularly in the assessment of mitochondrial dysfunction and tissue oxygenation. However, further research is needed to fully establish the clinical utility of the L/P ratio as a reliable biomarker for monitoring critically ill patients and guiding therapeutic interventions.

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> Koncentracija laktata i piruvata i njihov omjer kao marker za lokalnu ili sistemsku hipoksijsko-ishemijsku ozljedu

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Laktat i piruvat igraju ključnu ulogu u procjeni metaboličkog statusa kritično bolesnih pacijenata. U normalnim uvjetima, laktat se proizvodi anaerobnom glikolizom, a jetra i bubrezi odgovorni su za njegovu eliminaciju. Povišena razina laktata, poznata kao hiperlaktatemija, može nastati zbog različitih stanja, uključujući hipoksiju tkiva, oštećenu iskoristivost kisika i metaboličke poremetnje. Hiperlaktatemija je često povezana s nepovoljnim ishodima, osobito u kritičnim bolestima kao što su sepsa i šok. Laktička acidoza, koja se karakterizira povišenim razinama laktata i smanjenim pH krvi, dodatno pogoršava metaboličku acidozu i dovodi do višestrukog zatajenja organa ako se ne liječi na vrijeme. Omjer laktata/piruvata (L/P) potencijalni je pokazatelj za razlikovanje između hipoksijske i ne-hipoksijske hiperlaktatemije. Visok L/P omjer ukazuje na značajnu mitohondrijsku disfunkciju i oštećen metabolizam oksidacije, što često upućuje na težu prognozu. S druge strane, niži L/P omjer obično ukazuje na povoljniji ishod. Međutim, klinička korisnost L/P omjera ograničena je težinom mjerenja piruvata i njegovom ovisnošću o čimbenicima kao što su pH i redoks potencijal. Iako se mjerenja laktata rutinski provode u hitnim i intenzivnim uvjetima, postoji ograničen broj podataka o prognostičkoj vrijednosti L/P omjera. Nedavna istraživanja pokazala su da persistentna hiperlaktatemija s povišenim L/P omjerom tijekom prvih 24 sata kod septičnog šoka korelira s povećanom stopom smrtnosti i zatajenjem organa. Osim toga, istraživanja kritičnih stanja poput koronavirusa 2019 (COVID-19) sugeriraju da razine cirkulirajućeg piruvata mogu i predvidjeti ozbiljnost bolesti. Sveukupno, L/P omjer ima potencijal da bude vrijedan alat za praćenje kritično bolesnih pacijenata, ali potrebna su daljnja istraživanja da bi se potvrdila njegova šira klinička primjena.

Ključne riječi: *laktat, piruvat, omjer laktat/piruvat, hiperlaktatemija, kritična bolest, prognoza.*