

Lactate and hyperlactatemia revisited: an overview

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Introduction

In critically ill patients, elevated lactate levels are often used as a marker of illness severity. There is a vast body of literature correlating lactate with an overall worse outcome¹⁻³, however, it is important to remember that correlation does not necessarily imply causality. Furthermore, it is not yet clear whether giving a therapeutic implication to elevated lactate levels will improve patient outcome. Moreover, more recent literature suggests possible protective qualities of the lactate molecule against further injury.

In this narrative review, we address these issues by comparing the contemporary literature to the classic view of lactate as a metabolic waste product and marker of shock severity. Firstly, the metabolism of lactate will be described. Then, the causes of elevated lactate levels are reviewed and finally, the prognostic implications of elevated lactate and the evidence surrounding the use of lactate as a guide for therapeutic interventions will be discussed. The acid-base abnormalities resulting from lactate acidosis will not be reviewed in this article.

Metabolism

Relevant pathways

When discussing lactate, it should be noted that the lactate molecule has two stereo-isomers, namely L-lactate and D-lactate. D-lactate is produced in the gut when bacteria are exposed to large amounts of unabsorbed carbohydrates. Although D-lactate is not normally measured by routine laboratory tests, it should not be discarded entirely since it may enter the bloodstream and cause neurological symptoms³³. L-lactate is a metabolic product produced by our own cells which, as we will see in the following chapters, may be elevated in numerous situations.

The following equation is central in lactate metabolism and responsible for both the synthesis and breakdown of lactate:



As can be seen from the equation above, pyruvate plays a major role in lactate metabolism (Figure 1). The majority of pyruvate is produced by the Embden-Meyerhof pathway through anaerobic glycolysis, while a small contribution is made by other sources of pyruvate such as the pentose phosphate pathway and the alanine pathway. Subsequently, 90% is metabolised to acetyl-coenzyme A by pyruvate dehydrogenase, which then enters the oxygen dependent Krebs cycle for the generation of ATP (tricarboxylic acid pathway). Notably, nearly 10 % of pyruvate is metabolized to lactate even when sufficient oxygen is available. Finally, pyruvate can also be used as a substrate for gluconeogenesis (the Cori cycle) or undergoes transamination to alanine.

In anaerobic conditions, pyruvate cannot enter the Krebs cyclus due to insufficient oxygen, leading to a buildup of lactate as the much less efficient pyruvate-to-lactate pathway becomes the major energy source of our cells (Figure 2).

Under normal circumstances, blood pyruvate: lactate ratio is 10:1 and approximately 20 mmol lactate / kg bodyweight is produced daily, which results in a serum arterial lactate concentration of less than 2 mmol/l. Although lactate production increases substantially during maximal exercise, it is rapidly metabolized afterwards keeping blood levels stable⁴.

Both lactate production and clearance are catalyzed by lactate dehydrogenase (LDH) enzyme, a tetramere with 5 isoforms of which LDH-A and LDH-B are the most important. LDH-A is a cytosolic enzyme with high affinity for pyruvate and low affinity for lactate, and thus is responsible

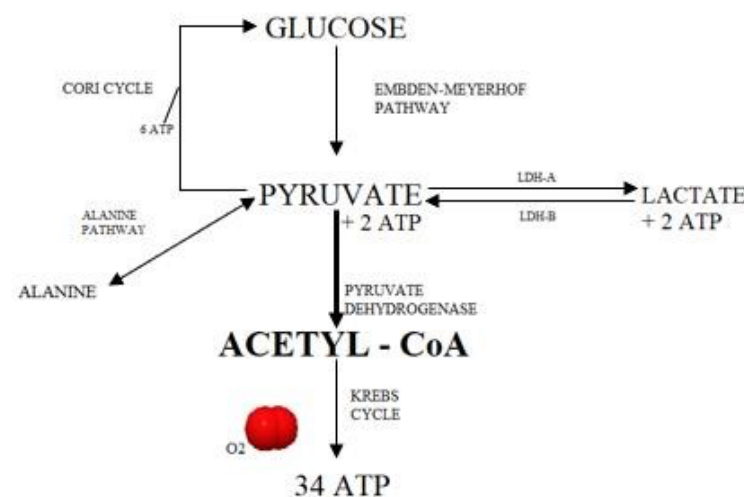


Fig. 1 — Schematic representation of different pathways concerning pyruvate metabolism in aerobic conditions. In the presence of sufficient oxygen, 90 % of pyruvate enters the Krebs cycle.

for the production of lactate. Of note, as a result of the presence of LDH-A in erythrocytes, samples for serum lactate measurements need to be kept on ice (thereby slowing the activity of the LDH enzyme) if the interval between blood sampling and analysis is more than 15 minutes.

LDH-B, on the other hand, has a high affinity for lactate and low affinity for pyruvate and is found in mitochondria. It is responsible for the clearance of lactate and the production of pyruvate. The produced pyruvate can enter the Krebs cycle and serve as a source of ATP through oxidative phosphorylation, with gluconeogenesis (the Cori cycle) and transamination as alternatives. The first pathway can occur in any cell that possesses mitochondria. The latter two only occur in the liver and kidney⁶. Consequently, the lactate molecule is able to serve as a fuel source.

Production, metabolism and elimination

In aerobic conditions, the major lactate producers are skeletal muscles (25%), skin (25%), brain (20%) and red blood cells (20%)⁵. The source of the remaining 10 % of lactate production is less clear, but most likely comprises the gut and, in certain conditions, the lung⁴.

In critically ill patients, lactate is also produced by other organs such as the splanchnic system, lungs and white blood cells. In physiological conditions, the production of lactate in the lungs is negligible, yet in septic patients, they become a major contributor to arterial lactate⁸. Since activated white blood cells mainly rely on anaerobic glycolysis for their energy production, infection and inflammation leads to significant lactate production⁹.

As mentioned above, lactate can serve as a fuel source to several organs, namely the heart,

brain and skeletal muscles. In resting conditions, the heart is a net lactate uptaker, which is almost entirely oxidized⁴. Interestingly, cardiac lactate metabolism seems to make a larger contribution to cardiac ATP production than glucose during stress situations. As myocardial oxygen needs and coronary blood flow increase, lactate becomes the primary fuel for the heart, accounting for up to 60% of cardiac energy requirements in one study¹⁷. Using carbon-labeled isotopes it has been shown that lactate contributes 15% in resting conditions and 30% during exercise to oxidative energy production while glucose only respectively contributes 8 and 14%¹⁸. Moreover, lactate contributes significantly to cardiac acetyl-CoA formation¹⁹, and Levy et al. showed that myocardial lactate deprivation is associated with decreased myocardial performance and outcome²⁰.

Traditionally, glucose is seen as the main fuel source for the brain. However, it has been shown that lactate also plays an important role as a cerebral energy source, mainly due to the astrocyte-to-neurone lactate shuttle. One study compared the relative contribution of lactate to the energy supply of the brain during rest and physical exercise receiving an exogenous lactate infusion and during rest without exogenous lactate. It found that while under basal conditions, lactate could account for 7% of cerebral energy requirements, during physical exercise with exogenous lactate infusion this could reach up to 27%²¹.

During strenuous exercise, skeletal muscles, though accounting for 25 % of lactate production, can also quickly become lactate consumers and thereby contribute to lactate elimination⁴. Several studies have shown that muscles metabolize both endo- and exogenous lactate as fuel¹⁰⁻¹⁴.

Under normal circumstances, the liver accounts for 70 % of lactate clearance, while the kidney and heart are responsible for respectively 20 and 10%⁷. Lactate uptake by the kidney comprises 20-30% of the total daily lactate uptake and, through the Cori cycle, this accounts for over 50% of renal gluconeogenesis. The effects of exercise on renal lactate metabolism are unknown¹⁵. Urinary excretion of lactate by is also possible when the renal lactate threshold (plasma lactate levels of 5-6 mmol/l) is exceeded¹⁶.

A revised view of hyperlactatemia

During most of the twentieth century, lactate was seen as a metabolic waste product, causing oxygen debt and muscle fatigue and contributing to tissue damage caused by acidosis. Even though evidence of beneficiary aspects of the lactate molecule are long-standing, this classic view still resonates in

most clinician's perception of elevated lactate levels. Indeed, lactate is an important intermediary product in various metabolic processes, aids the process of wound repair and tissue regeneration and, as shown above, is an important energy source for vital organs, especially during exercise. Moreover, through lactate shuttles, energy supply by the lactate molecule is facilitated²⁵.

Lactate shuttles mediate the rapid transport of the lactate molecule from cell-to-cell through monocarboxylic acid transporters (MCTs) and thereby greatly influence lactate metabolism and clearance both in aerobic and anaerobic conditions^{25,26}. This form of intercellular transport has been described in skeletal muscles, red blood cells, astrocytes (the astrocyte-neuron and lactate-alanine shuttle) and sperm cells (the spermatogenic lactate shuttle)²⁷⁻²⁹.

In cases of either systemic or regional hypoperfusion, pyruvate cannot enter the Krebs cycle due to insufficient oxygen. Lactate is then metabolized by lactate dehydrogenase via an alternative pathway, which explains why lactate rises in the presence of tissue hypoxia. Additionally, lactate clearance is impaired due to mitochondrial dysfunction in shock states. Subsequently, insufficient systemic oxygen delivery is often seen as the sole culprit of hyperlactatemia. However, there are other mechanisms besides oxygen deficiency that favour lactate production such as microcirculatory dysfunction, increased aerobic glycolysis and impaired activity of the pyruvate dehydrogenase enzyme.

Interestingly, the rate limiting step in aerobic glucose metabolism is the pyruvate dehydrogenase enzyme, meaning that in situations of increased pyruvate load, enzymatic saturation occurs. As excess pyruvate is metabolised by lactate dehydrogenase, hyperlactatemia may occur as a result of increased pyruvate levels in the presence of sufficient tissue oxygenation. In other words, lactate formation does not necessarily equal oxygen debt. Elevated pyruvate levels result from increased aerobic glycolysis, which in turn is mostly caused by hyperglycemia and β_2 -adrenoreceptor stimulation.

The effect of β_2 -adrenoreceptor stimulation on arterial lactate levels is mediated through the Na⁺-K⁺-ATPase pump. β_2 -stimulation increases cAMP production, which stimulates glycogenolysis and thereby provides ATP for the Na⁺-K⁺-ATPase pump. The latter generates ADP which, via phosphofructokinase stimulation, reactivates glycolysis. Ultimately this leads to elevated pyruvate levels which, as mentioned above, increases lactate production^{23,24}.

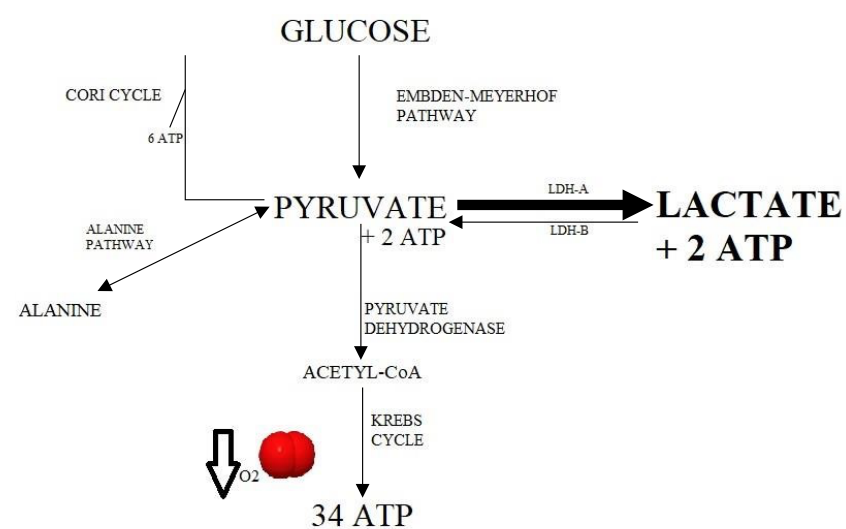


Fig. 2 — Schematic representation of different pathways concerning pyruvate metabolism in anaerobic conditions. In the absence of sufficient oxygen, ATP is mainly generated through metabolism of pyruvate to lactate by the LDH-A enzyme.

Interestingly, one study in 100 patients admitted to the Intensive Care Unit with various forms of shock state, found that a higher increase in arterial lactate concentration when using epinephrine (and thus an appropriate metabolic response to β 2-adrenoreceptor stimulation) was associated with a better prognosis, suggesting that elevated lactate is rather an adaptive, protective mechanism instead of a damaging one²⁴.

Causes of lactic acidosis

In 1976, Cohen and Woods first made the distinction between elevated L-lactate levels in the presence of either insufficient or sufficient global oxygen delivery, respectively termed type A and type B lactic acidosis. Table I gives an overview of the main causes of lactic acidosis, with a brief description of their presumed mechanism. The vast majority of cases of lactic acidosis are related to hypovolemic shock, cardiogenic shock, sepsis and severe trauma³².

Type A lactic acidosis

In type A lactic acidosis, there is insufficient oxygen delivery relative to tissue oxygen demand. This results in tissue hypoxia leading to an increased lactate production (as a metabolic alternative to the Krebs cycle) and a decreased clearance of lactate due to failing mitochondrial oxidation. This oxygen deficit can be global, regional (such as compartment syndrome or limb ischemia), or even due to microcirculatory dysfunction. Elevated lactate levels reflect the degree of tissue hypoxia in these cases. Animal studies support the hypothesis that lactate levels rise when reducing systemic oxygen delivery below a critical point and the correlation between hyperlactatemia and low systemic oxygen delivery, both during exercise and circulatory shock, has been replicated in human subjects as well³⁵⁻³⁷.

Most studies on prognostic value and therapeutic implications within this group have been conducted in the trauma population. Trauma patients are subjected to multiple possible mechanisms associated with insufficient systemic oxygen delivery and thus type A lactic acidosis. These include hemorrhagic, cardiogenic and obstructive shock (namely tension pneumothorax and cardiac tamponnade).

Type B lactic acidosis

Type B lactic acidosis occurs exclusively in the presence of aerobic glycolysis through a mechanism called stimulated glycolysis. As mentioned above,

hyperglycemia and β 2-adrenoreceptor stimulation can lead to a state of stimulated glycolysis and consequently an increase in lactate production in the absence of tissue hypoxia⁸⁶. Furthermore, physical stress response results in higher energy requirements, which are met by β 2-adrenoreceptor stimulation. Finally, cytokines strongly stimulate cellular glucose uptake and subsequently aerobic glycolysis in inflammatory states. These mechanisms all lead to a raised pyruvate level, overwhelming the pyruvate dehydrogenase enzyme so that the excess pyruvate is metabolised by lactate dehydrogenase. Though lactic acidosis follows, blood pyruvate:lactate ratio stays within the normale range (10:1).

Type B lactic acidosis can further be divided into 3 types: associated with underlying disease (B₁), drugs and toxins (B₂) or inborn errors of metabolism (B₃). Two of the most common causes of type B lactic acidosis, namely sepsis and malignancy, are discussed below.

Sepsis

Most evidence concerning lactate comes from septic patients, in whom lactate levels are elevated in two thirds of cases. In the past, elevated lactate levels in sepsis have mainly been attributed to tissue hypoxia and were thus regarded as type A lactic acidosis. However, there is a growing body evidence that this might rather be a type B lactic acidosis⁷⁵. If hyperlactatemia resulted from tissue hypoxia, one would expect that increasing oxygen delivery would result in lower lactate levels and a better outcome. Nevertheless, trials targetting a supra-normal oxygen delivery showed no improvement in lactate levels⁸⁷.

Furthermore, it has been shown that beta-blocking therapy with esmolol is capable of decreasing lactate levels during sepsis. This is counterintuitive since one would expect beta-blocking therapy to be associated with a decreased oxygen delivery due to a decreased cardiac output. This observation likewise implies that lactate levels in sepsis are not solely dependent on the level of tissue oxygen delivery⁸⁸.

Opdam and Bellomo showed a substantial lactate production by the lung during sepsis. It is improbable that this would be the result of hypoxia since the lung bathes in oxygen and receives full cardiac output⁸⁹. Increased aerobic glycolysis through β 2-adrenoreceptor stimulation, activated cytokines and increased metabolic rate could explain the elevated lactate levels. Other possible mechanisms include pyruvate dehydrogenase inhibition, reduced lactate clearance, mitochondrial and microcirculatory dysfunction⁹⁰.

Table I. — Causes and mechanisms of elevated lactate levels.

Causes of lactic acidosis	
Cause	Main mechanism
Type A lactic acidosis	
Sepsis, trauma, cardiogenic and hypovolemic shock	Tissue hypoxia
Hypoxemia	Decreased O ₂ delivery if PaO ₂ < 30 mmHg (34)
Anemia	Decreased O ₂ delivery if Hb < 5 g/dl (34)
Carbon monoxide poisoning	Decreased O ₂ delivery and interference with oxidative phosphorylation
Seizures, exercise, shivering	Relative tissue hypoxia due to increased O ₂ requirements
Distributive shock	Microcirculation derangements
Regional ischemia: intestinal / limb ischemia, compartment syndrome, necrotizing fascitis, burns	Tissue hypoxia
Cardiac arrest	Tissue hypoxia
Type B lactic acidosis	
B ₁ (underlying disease)	
Sepsis	β ₂ -adrenoreceptor stimulation
Asthma	β ₂ -adrenoreceptor stimulation (both endo- and exogenous)
Alkalosis	6-phosphofructokinase stimulation
Pheochromocytoma	β ₂ -adrenoreceptor stimulation
Liver disease and resection	Increased production, reduced clearance
Diabetes mellitus	Unclear
Diabetic ketoacidosis	Dehydration and tissue hypoperfusion
	D-lactic acidosis, presumably due to methylglaxal accumulation
Cancer	Warburg effect, tumor tissue hypoxia, decreased lactate clearance with liver metastasis
Thiamine deficiency	Pyruvate dehydrogenase activity impairment
Kidney failure	Reduced clearance
B ₂ (drugs and toxins)	
Antiretroviral agents	Oxidative phosphorylation interference
Propofol	Oxidative phosphorylation interference
Metformin	Oxidative phosphorylation interference
Cocaine	β ₂ -adrenoreceptor stimulation
Toxic alcohols (excessive ethanol, methanol, ethylene glycol, diethylene glycol)	Oxidative phosphorylation interference
Propylene glycol	Lactate normal product of metabolism
Salicylates	Oxidative phosphorylation interference
Cyanides	Oxidative phosphorylation interference
β ₂ -agonists	β ₂ -adrenoreceptor stimulation
B ₃ (inborn errors of metabolism)	
Glucose-6-phosphatase, fructose 1-6disphosphatase, pyruvate dehydrogenase, pyruvate carboxylase deficiency	Reduced metabolisation of pyruvate through other pathways than the lactate pathway (Such as the Krebs and Cori cycle)

Malignancy

Cancer cells use lactate produced through anaerobic glycolysis as their main fuel source, even under normal circumstances. This phenomenon which is called the Warburg effect can sometimes lead to

clinically relevant hyperlactatemia. Moreover, lactate is proving to be a crucial signaling molecule in the microenvironment of cancer cells, playing an important role in tumor progression. Pharmacological treatment strategies aimed at lactate are currently

in phase I/II trials¹⁰⁸. Furthermore, malignancy can lead to hyperlactatemia through vitamin B1 (thiamine) deficiency as this is an essential cofactor in the pyruvate dehydrogenase complex. Several case reports were published in which patients who presented with lactic acidosis as a first symptom of malignancy were treated with intravenous thiamine administration, which resulted in normalization of lactate levels¹⁰⁹. Hyperlactatemia in malignancy is most commonly seen with hematologic malignancies such as leukemia. However, it is also a possibility with solid, especially aggressive, tumors.

Prognostic implications of elevated lactate

Studies have shown that elevated serum lactate levels are directly correlated to poorer outcome variables in Intensive Care Unit patients, even when macrocirculatory hemodynamic parameters were still within normal ranges. In other words, lactate levels rise before macrocirculatory parameters deteriorate, suggesting the concept of occult hypoperfusion^{38,39}.

The prognostic value of elevated lactate levels has mainly been studied in trauma and sepsis patients, and during or after cardiac surgery. Therefore, these specific groups will be discussed separately.

Trauma

Elevated lactate levels have an important prognostic value in trauma patients. Prehospital lactate levels are correlated with injury severity and more importantly with in-hospital mortality⁴²⁻⁴⁴. This prognostic information is deemed superior than the patient's vital signs. Specifically, the change in lactate levels between the prehospital measurement and the first in-hospital measurement was independently correlated with mortality. In other words, failure to clear the excess lactate production is likely to be more significant than the observation of one isolated elevated value. Other studies also confirm the prognostic value of in-hospital lactate levels after trauma⁴⁵⁻⁵³. Similarly, in non-traumatic settings in the emergency department, lactate levels have prognostic value and are deemed useful in risk stratification^{41,54-58}.

An interesting area of study within the trauma population are those with traumatic brain injury. In the section of metabolism we introduced the idea of lactate as a fuel source for the brain. This seemingly opposes the well-known concept of "glucose paradox of cerebral ischemia", first described in 1970⁶¹. In summary, although glucose was considered to be the main fuel source for the brain,

investigators observed that neuronal damage during cerebral ischemia was more pronounced in patients with hyperglycemia, presumably due to a higher rate of glycolysis and thus lactate levels. This is still cited as one of the main arguments for the potential harmful effects of lactate (irrespective of the underlying cause). However, recent in vitro studies suggest that lactic acid and glucose may actually be protective in cerebral ischemia⁶²⁻⁶³. Payne et al. suggested that a rise in cortisol rather than lactic acid might be the culprit⁶⁴. This observation could explain why steroid therapy following traumatic brain injury actually significantly increased mortality⁶⁵.

The evidence for lactate as a protective mechanism for the brain keeps growing. In 2010, Cureton et al. showed that patients with the same severity of traumatic brain injury had a better outcome (measured as mental status on discharge) when lactate levels were higher⁶⁶. These observations have led to trials of exogenous lactate infusions in traumatic brain injury. In 2009 a trial showed improved intracranial pressure (ICP) control in the lactate group compared to an equivalent osmotic load of mannitol. In addition, long term outcome based on the Glasgow Outcome Score was significantly better⁶⁷. In 2013, the same authors suggested a beneficial effect of exogenous lactate for the prevention of raised ICP episodes⁶⁸. A comparison with sodium chloride 3% also showed better neurocognitive function in the lactate group⁶⁹. In other words, besides convincing evidence that hyperlactatemia is not harmful in itself, these studies using exogenous lactate could also help support the hypothesis that endogenous hyperlactatemia is an adaptive and protective mechanism. This point is further supported by studies using dichloroacetate, a molecule that shifts metabolism towards oxidative phosphorylation through the activation of the mitochondrial pyruvate dehydrogenase complex, which results in a decreased lactate production. Although trials have indeed shown a significant decrease in lactate concentrations through dichloroacetate administration, no influence on outcome was found^{70,71}.

Cardiac surgery

The prognostic value of elevated lactate levels in cardiac surgery has been extensively studied and worse outcomes and higher mortality have consistently been reported as lactate levels rise^{37,72-74,76-79}.

However, as mentioned in the section on metabolism, there is compelling evidence that lactate serves as a fuel source for the heart, especially in stress situations. Although early

studies suggested that the lactate molecule depresses cardiac inotropy⁸⁰, more recently it has been shown that lactate deprivation actually resulted in decreased cardiac performance during cardiac surgery, which is the expected result considering the metabolic physiology⁸¹. Furthermore, it has been suggested that lactate may improve cardiac efficiency after hemorrhagic shock. In order to investigate the effect of lactate on cardiac function, multiple studies using exogenous lactate infusions were set up (similar to studies in patients with traumatic brain injury). In a pilot study in 2014, half-molar sodium lactate (containing 0.5 mmol/l lactate) was infused in patients with acute heart failure, resulting in elevated cardiac output, though having no influence on mortality⁸². Studies comparing hyperosmolar sodium lactate with either hydroxyethyl starches or Ringer's lactate also showed a significantly higher cardiac index with a lower infused volume, suggesting a direct effect of lactate on cardiac output^{83,84}.

Sepsis

There is a vast body of literature linking elevated lactate levels in sepsis to worse outcomes^{57,91-93}. Using lactate levels patients can be stratified in different mortality groups, with a higher lactate resulting in higher mortality⁵⁶. Early lactate clearance is associated with improved outcome and thus might serve as a marker for adequate global hemodynamic resuscitation⁹⁴⁻⁹⁷. In patients with suspected infection, elevated lactate levels resulted in higher 28-day mortality, even in the absence of abnormal vital signs⁵⁵. In other words lactate levels rise before macrocirculatory parameters deteriorate and may thus serve as an early warning sign.

Evidence surrounding the use of lactate as a guide for therapeutic interventions

The relationship between oxygen deficit and raised lactate levels, and the vast literature surrounding the prognostic value of lactate levels have led to the idea that lactate levels could somehow be useful in guiding therapy in selected patients¹⁶.

Treatment obviously depends on the exact cause of tissue hypoperfusion and consists of tailored hemodynamic management such as vasopressors, inotropic agents, fluids, adequate ventilation and oxygenation and blood transfusion. Even attention to the microcirculation might be warranted in certain cases. Quite often in clinical practice, lactate acidosis is unfairly attributed to hypovolemia without considering other causes of increased lactatemia.

A detailed discussion of hemodynamic support falls outside the scope of this article. However, it

is important to stress that one should always aim to treat the underlying cause of lactic acidosis. Although fluid therapy may be adequate if the patient is hypovolemic, hyperlactatemia in itself should not automatically trigger fluid administration, since this may simply cause dilution of lactate levels without improving outcome if inadequate tissue perfusion is not the true cause for the observed hyperlactatemia.

While some observational studies suggest the use of lactate to guide resuscitation there is almost no prospective evidence to support this claim⁴⁰.

In 2010 Jansen et al. published the first and only randomized controlled trial looking at lactate-based resuscitation in a heterogeneous group of patients with presumed type A lactic acidosis⁴¹. In the lactate group the goal was a decrease in serum lactate levels of 20% every 2 hours, using a well-defined protocol. The control group consisted of resuscitation based on heart rate, blood pressure, central venous pressure, urinary output, arterial oxygen saturation, mixed venous saturation, hemoglobin level and subjective assessment of the peripheral circulation. Shorter weaning from ventilation, more rapid discharge from the Intensive Care Unit and lower mortality was found in the lactate group, and this group also received a significantly higher amount of fluids and vasodilators. While encouraging, there are some important limitations that need to be taken into account when interpreting these results. The goal of achieving a 20% or more decrement every 2 hours was met in both the lactate based and the control group. In other words, despite using more fluids and vasodilators, lactate clearance was not faster. Furthermore, septic patients were included in the trial, while there is increasing evidence that type B lactic acidosis might be more important in sepsis⁷⁵. The authors conclude that their results provide insufficient evidence to recommend lactate-based therapy.

As this study was conducted in a heterogeneous group of patients, it might be of interest to look to specific situations where type A lactic acidosis is the most probable mechanism responsible for elevated lactate levels, i.e. trauma and cardiac surgery.

Trauma

Regarding the use of lactate levels as a therapeutic aid in trauma patients, the evidence is less compelling compared to its prognostic value. According to Okorie et al., the value of prehospital lactate measurements mainly resides in its ability to trigger specific treatment algorithms¹⁶. There is only one prospective study to date investigating

the use of a treatment algorithm based on lactate levels⁶⁰. In this study, elevated venous lactate levels (defined as 2.5 mmol/l or greater) activated the Advanced Trauma Life Support (ATLS) treatment, subsequently implying an early trauma surgeon consult. Although this approach resulted in statistically significant lower mortality, this improved outcome may merely reflect the beneficial effect of an earlier surgeon consult. Furthermore, bearing in mind the concept of occult hypoperfusion, the true benefit of this strategy could lie in an improved screening for tissue hypoxia. Finally, in this study lactate levels were simply used to identify patients in need of more aggressive therapy, while the treatment measures were the classic ATLS protocols. Although we believe this study definitely proves the importance of early lactate measurements, it is erroneous to consider this as true lactate-based therapy.

Cardiac surgery

Only one trial has been published to date concerning lactate-guided resuscitation during cardiac surgery. No difference in mortality was observed⁸⁵.

Sepsis

To date, only a handful of trials exploring goal-directed therapy in sepsis (including but not limited to resuscitation based on lactate levels) have been published. In 2001 Rivers et al. published their landmark trial showing a significantly better outcome in patients with severe sepsis using early goal-directed therapy. Therapeutic interventions were done based on central venous pressure, mean arterial pressure and mixed central venous oxygen saturation. While lactate levels were significantly lower in the early goal-directed group, elevated lactate in itself had no therapeutic implications. In 2010 Jones et al. repeated Rivers’ trial using lactate clearance instead of mixed venous central oxygen saturation as a trigger for resuscitation therapy in septic patients⁹⁸. In this study, no mortality benefit was found in the lactate group, whereas Lyu et al. did find a mortality benefit when using lactate-clearance guided therapy⁹⁹. We had to wait until 2014 for larger, multicenter randomized controlled trials. The investigators of the ARISE and ProCESS trial found no mortality benefit in the early goal-directed therapy group compared to standard care^{100,101}, and these results were confirmed in the ProMISe trial in 2015¹⁰².

Note that in the same year as the Jones study, Jansen et al. did find a mortality benefit for using elevated lactate levels as a therapeutic guide when resuscitating patients with presumed type A lactic acidosis, including septic patients⁴¹. Taking

into account the pathophysiological mechanisms behind type A and type B lactic acidosis, these contradictory results could indicate that lactate-guided resuscitation might be more beneficial in type A lactic acidosis where inadequate tissue oxygenation is present.

Three meta-analyses have been published concerning early goal directed therapy in septic patients. Gu et al. found a survival benefit in the early goal-directed therapy group, however this analysis was published before the ARISE en ProCESS trials, thus omitting substantial evidence to the contrary¹⁰³. A meta-analysis including these important trials found no mortality benefit and even a worse outcome in the early goal-directed group¹⁰⁴. Lee et al. found a mortality benefit in the in early goal-directed group when taking into account both observational studies and randomized trials¹⁰⁵. However, in a subgroup analysis of only randomized controlled trials, no benefit was found. Finally, the most recent meta-analysis in 2017 by the PRISM group confirmed once again that no improvement in outcome could be achieved in the early goal-directed group¹⁰⁶.

The most recent surviving sepsis campaign guidelines states that overall there’s no reason to either favor or avoid early goal-directed therapy¹⁰⁷. However, the guidelines suggest “guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion”. This is somewhat surprising since guiding resuscitation based on lactate is a form of early goal-directed therapy, which overall has no proven benefit. Furthermore, we have shown that there is ample evidence suggesting lactate levels in sepsis do not necessarily reflect the degree of tissue hypoperfusion.

Conclusions

Compelling evidence indicates that lactate measurements can be used as a prognostic tool as higher lactate levels are clearly associated with worse outcome and higher mortality. There seems to be a dose-response relationship between lactate levels and mortality, thus lactate can serve as a parameter for underlying disease severity. This has been shown in many different clinical situations including but not limited to the heterogenous ICU population, the emergency department, after major surgery, and in sepsis patients. We believe that lactate can be especially helpful as a screening tool for occult hypoperfusion as it can accurately help us to identify at-risk patients in an early stage. Notably, the prognostic value of lactate levels has been confirmed in patients with type A as well

as type B lactic acidosis (respectively with and without tissue hypoperfusion).

Although these observations have led to the idea that lactate may serve as a guide for global hemodynamic resuscitation, the evidence supporting this claim is controversial at best. Most studies concerning lactate-based early-goal directed therapy have been conducted in sepsis patients and showed no mortality benefit to this strategy⁹⁸⁻¹⁰⁶. A 2010 study in patients with presumed type A lactic acidosis, however, did find a mortality benefit to lactate-based therapy⁴¹. Taking into account the pathophysiological mechanisms behind type A and type B lactic acidosis, and the growing evidence that type B lactic acidosis is most prominent in septic patients, these contradictory results could indicate that lactate-guided resuscitation might be more beneficial in type A lactic acidosis where inadequate tissue oxygenation is present.

Before even considering using lactate as a guide for therapy, a thorough diagnostic workup is imperative, including additional tests to distinguish between type A and type B lactic acidosis. It is crucial to understand that hyperlactatemia does not always equal tissue hypoxia, and lactate level in itself does not correlate well with tissue hypoxia¹¹⁰.

Furthermore, there is a growing body of literature suggesting that elevated lactate levels are a compensatory, protective mechanism rather than solely an accumulation of metabolic waste product. Some studies even found a better prognosis in patients with higher lactate levels when underlying disease severity was the same. Consequently, if hyperlactatemia has a metabolic function, lowering lactate levels would not be a sensible therapeutic goal. The hypothesis that lactate could have protective qualities has led to preliminary trials using exogenous lactate as a therapeutic intervention, with promising results.

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