Lactic acidosis, hyperlactatemia and sepsis

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ABSTRACT

Among hospitalized patients, lactic acidosis represents the most common cause of metabolic acidosis. Lactate is not just a metabolic product of anaerobic glycolysis but is triggered by a variety of metabolites even before the onset of anaerobic metabolism as part of an adaptive response to a hypermetabolic state. On the basis of such considerations, lactic acidosis is divided into two classes: inadequate tissue oxygenation (type A) and absence of tissue hypoxia (type B). Lactic acidosis is characterized by non-specific symptoms but it should be suspected in all critical patients who show hypovolemic, hypoxic, in septic or cardiogenic shock or if in the presence of an unexplained high anion gap metabolic acidosis. Lactic acidosis in sepsis and septic shock has traditionally been explained as a result of tissue hypoxia when whole-body oxygen delivery fails to meet whole body oxygen requirements. In sepsis lactate levels correlate with increased mortality with a poor prognostic threshold of 4 mmol/L. In hemodynamically stable patients with sepsis, hyperlactatemia might be the result of impaired lactate clearance rather than overproduction. In critically ill patients the speed at which hyperlactatemia resolves with appropriate therapy may be considered a useful prognostic indicator. The measure of blood lactate should be performed within 3 h of presentation in acute care setting. The presence of lactic acidosis requires early identification of the primary cause of shock for the best appropriate treatment. Since most cases of lactic acidosis depend on whole-body oxygen delivery failure, the maximization of systemic oxygen delivery remains the primary therapeutic option. When initial resuscitation does not substantially or completely correct lactic acidosis, it is also essential to consider other causes. The treatment of acidosis with buffering agents (specifically bicarbonate) is generally advocated only in the setting of severe acidosis. Ongoing research into lactate clearance and probable noninvasive surrogate measures may add further insight into outcome-based practices.

Introduction

Lactic acidosis is a state of acidosis determined by an elevated plasma lactate concentration. It is a type of anion gap metabolic acidosis and may result from several conditions.[1,2] Among hospitalized patients, lactic acidosis represents the most common cause of metabolic acidosis. The normal blood lactate concentration in unstressed patients is 0.5-1 mmol/L, whereas lactic acidosis is diagnosed when the serum concentration of lactate or lactic acid is persistently 5 mmol/L or greater and serum pH <7.35.[3] Lactate arises from the metabolism of glucose and its concentration derived by the balance between lactate production and lactate metabolism, normally constant in the body.

Lactic acid is produced by cytosolic glycolysis and by the reduction of pyruvate. Both molecules are interconvertible and the reaction is catalyzed by the enzyme lactate dehydrogenase in the presence of nicotinamide adinine dinucleotide/nicotinamide, as reported in the following formula:

$$\text{Pyruvate} + \text{NADH} + \text{H}^+ = \text{lactate} + \text{NAD}^+ \quad (1)$$

This is a reversible reaction that promotes lactate synthesis with the lactate-to-pyruvate ratio that is normally at 25:1. Lactate synthesis increases when the rate of pyruvate formation in the cytosol exceeds its rate of use by the mitochondria. This happens when a rapid increase in metabolic rate occurs or when oxygen delivery to the mitochondria declines, such as in tissue hypoxia. Lactate synthesis may also occur when the rate of glucose metabolism exceeds the oxidative capacity of the mitochondria, as observed with administration of catecholamines or errors of metabolism.

In physiological conditions pyruvate enters into the Krebs cycle and is catalyzed by pyruvate dehydrogenase, limited by thiamine deficiency or when suffi-

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cient oxygen is not available (Figure 1). In such cases, the Krebs cycle cannot metabolize pyruvate that therefore is switched to lactate. Importantly, in patients with sepsis, increased glycolytic flux results in increased pyruvate production and hence lactate production, while keeping a normal lactate:pyruvate ratio. At rest, red blood cells, brain and skin are major sources of lactic acid, whereas during exercise skeletal muscles release a significant amount of lactic acid.

Lactic acidosis has been traditionally interpreted as a biological marker of tissue hypoxia. However, lactate is not just a metabolic product of anaerobic glycolysis. In fact, its production is triggered by a variety of metabolites even before the onset of anaerobic metabolism as part of an adaptive response to a hypermetabolic state, such as sepsis.[4]

In 1976, Cohen and Woods classified hyperlactatemia into two categories: lactic acidosis associated with clinical evidence of inadequate tissue oxygenation (type A) and hyperlactatemia in which clinical evidence of tissue hypoxia was absent (type B).

Type B hyperlactatemia was further subdivided into three categories: B1, hyperlactatemia associated with underlying diseases such as liver failure (B1); hyperlactatemia secondary to drugs or toxins (B2); hyperlactatemia caused by inborn errors of metabolism (B3) (Table 1).[5]

Clinical presentation

Lactic acidosis is characterised by non-specific symptoms. It should be suspected in all critical patients who show hypovolemic, hypoxic, in septic or cardiogenic shock or in the presence of an unexplained high anion gap metabolic acidosis. Tissue hypoperfusion (peripheral vasoconstriction), hypotension, oliguria/anuria and altered sensorium are frequent clinical signs of lactic acidosis.

Frequent important causes of lactic acidosis

A further classification of lactic acidosis could be made considering the pathophysiological aspect underlying the determination of lactic acid accumulation. As reported in Table 2 the main categories are hypoxic and no-hypoxic causes.[6] Among the most frequent hypoxic causes, we can find ischemia, severe anemia, cardiac arrest and shock, whereas sepsi, delayed clearance, renal or hepatic dysfunction and thiamine deficiency are more frequent among those non-hypoxic.

Vigorous exercise

The extent of lactic acid increases depending on the type and severity of exercise, such as a prolonged generalized tonic-clonic seizures.

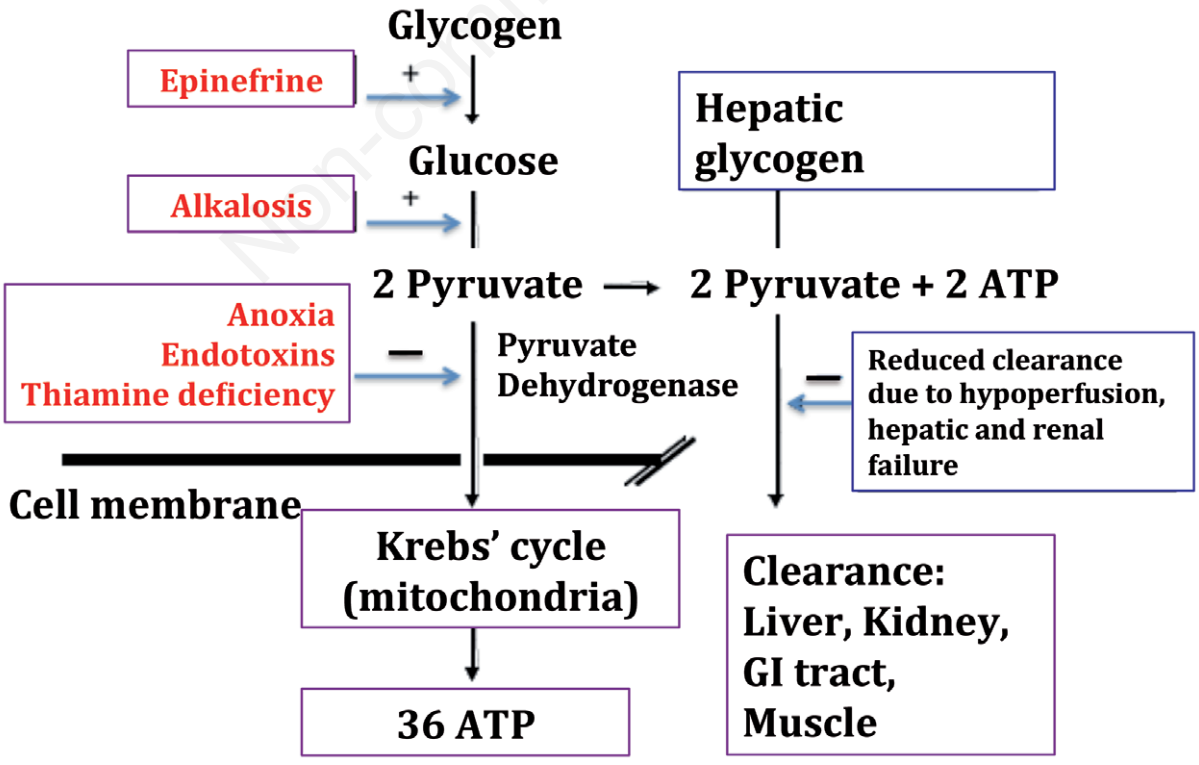

Figure 1. Lactate production and factors influencing serum lactate levels.

Tissue hypoxia

It is the predominant cause of lactic acidosis in critically ill patients. Prolonged hypoxia will lead to overproduction and underutilization of lactic acid leading to lactic acidosis. Cardio-respiratory arrest and similarly patients with acute left ventricular failure with pulmonary edema may develop acidosis due to reduced tissue perfusion and respiratory acidosis due to respiratory failure. Patients with advanced chronic obstructive airway disease have chronic compensated respiratory acidosis and they seldom show lactic acidosis.

Table 1. Causes of lactic acidosis - Cohen and Woods' classification.

Type A (clinical evidence of tissue hypoxia)
• Shock (septic, hypovolemic, obstructive, cardiogenic, combinations, rare kinds)
• Regional hypoperfusion (mesenteric, limb ischemia)
• Severe hypoxemia
• Severe anemia
• Carbon monoxide, cyanide, iron poisoning
• Severe muscle activity (exercise, seizures, asthma)
Type B (no clinical evidence of tissue hypoxia)
B1 (association with an underlying disease)
• Liver disease
• Sepsis
• Diabetes mellitus
• Malignancy
• Pheochromocytoma
• Thiamine deficiency
B2 (drugs/toxins)
• Biguanides
• Epinephrine, terbutaline, other adrenergic agonists
• Ethanol, methanol, ethylene glycol, propylene glycol
• Propofol
• Nitroprusside, inhaled nitric oxide
• Fructose
• Sorbitol
• Salicylates
• Acetaminophen
• Isoniazid
• Linezolid
Miscellaneous
• D-lactic acidosis
• Hypoglycemia

Carbon monoxide poisoning

Carbon monoxide binds to hemoglobin and as its affinity for hemoglobin is 40 times more than that of oxygen, it leads to tissue hypoxia and lactic acidosis.

Drugs and toxins

Ethanol oxidation increases the conversion of pyruvate to lactate and decreases the clearance of lactate. Prolonged *metformin* increases glycolysis in peripheral tissues decreasing pyruvate oxidation and hepatic lactate clearance. *Epinephrine* enhances hepatic glycogenolysis and glycolysis to lactate and reduces pyruvate utilization resulting in lactic acidosis especially in massive doses.

Terminal cirrhosis or hepato-cellular failure

Due to poor utilization of lactate and altered metabolism.

Neoplastic diseases

In patients affected by leukemia, tumor cells produce a large amount of lactate.

Lactic acidosis in sepsis

Sepsis is a fatal syndrome caused by severe infection. Severe sepsis is defined as the presence of one or more organ system dysfunction in the context of sepsis. Organ dysfunction includes pulmonary and hematologic abnormalities, neurologic disorder, renal dysfunction, liver or cardiac failure or hypo-perfusion with lactic acidosis. Septic shock is defined as the presence

Table 2. Pathophysiological classification of lactic acidosis.

Hypoxic	Non-hypoxic
Shock, cardiac arrest	Delayed clearance
Severe anemia	Renal or hepatic dysfunction
Global hypoxia	Sepsis, thiamine deficiency, catecholamine excess, alcoholic and diabetic ketoacidosis
Carbon monoxide poisoning	Uncoupling of oxidative phosphorylation
Respiratory failure, severe asthma, COPD, asphyxia	Cyanide, salicylates, methanol and ethylene glycol metabolites, antiretroviral drugs, valproic acid, biguanides, INH
Regional hypoperfusion	Accelerated aerobic glycolysis
Limb or mesenteric ischemia	Increased effort, sepsis, seizures, large fructose loads, malignancies

COPD, chronic obstructive pulmonary disease; INH, isoniazid. *Adapted from Gunnerson and Sharma, 2010.*[6]

of sepsis and refractory hypotension in which intravenous fluid administration alone is insufficient to maintain the hemodynamic of the patient.[7] Sepsis, with a mortality rate of 48.4%, is a leading cause of hospital mortality in adult patients,[8] while its incidence of 76-110 cases/year per 100,000 shows an increasing trend.[9]

The management of sepsis patients should include timely patient identification and diagnosis of underlining causes. Many studies show that initial or persistent hyperlactatemia is associated with adverse outcome, but no clear-cut point is evident. It sufficiently demonstrated that an increased blood lactate concentration is a powerful predictor of mortality in critically ill patients. In the past century, Weil and colleagues demonstrated an exponential increase in the mortality of critically ill patients with increasing blood lactate concentrations.[10,11] The mortality increases linearly above a lactate concentration of approximately 1 mmol/L and this association is independent of organ dysfunction or the presence of shock.

Lactic acidosis in sepsis and septic shock has traditionally been explained as a result of tissue hypoxia when whole-body oxygen delivery fails to meet whole body oxygen requirements.[12] In patients with sepsis, the resting metabolic rate is increased, leading to increased metabolism of glucose. Glycolytic flux can exceed that capacity of pyruvate dehydrogenase to catalyze conversion of pyruvate into acetyl coenzyme A. Consequently, pyruvate is inevitably converted into lactate by lactate dehydrogenase. Increased endogenous epinephrine and norepinephrine concentrations seem to determine an augmentation of sodium-potassium-adenosine triphosphatase (Na+ -K+-ATPase) activity by B2-receptor stimulation[13] since B2 antagonist and (Na+ -K+-ATPase) inhibitors determine a reduction of lactic acid production in septic shock.[14]

Lactate levels correlate with the presence of tissue hypoperfusion in shock and with increased mortality. Serum lactate levels above 4 mmol/L were associated with a survival of only 11% in critically ill patients in the Intensive Care Unit (ICU) after 24 h[15] and in patients with sepsis: such threshold is a useful marker of the severity of the disease with an associated higher risk of death.[16] Further studies have demonstrated an association between a 12-h rise in lactate concentration above 2.5 mmol/L and multisystem organ failure.[17] On the basis of previous data an increase in the lactate:pyruvate ratio in sepsis has been suggested as marker of tissue hypoxia.[18] However, trials aiming to increase oxygen delivery to meet potential unmet oxygen demand did not improve survival and may have increased mortality.[19] This apparent discrepancy should be partially explained considering the differences between the early resuscitation and the postresuscitation phase. Recent randomized controlled trials (RCT) showed that several resuscitation protocols, obtaining an early resuscitation with the correction of volume, blood pressure and oxygen tissue saturation, reduced mortality of septic shock from 60% to 20%.[20,21] These results suggest that, in the early resuscitation phase of septic shock, lactic acidosis production mainly came from anaerobic metabolism.

However, inadequate whole-body oxygen delivery is often not the full explanation for ongoing hyperlactatemia. In a prolonged septic shock, lactic acidosis could be explained by an impaired tissue oxygen extraction due to the dysfunction of microcirculation secondary to, endothelial inflammatory processes.[22] During sepsis, this critical oxygen extraction ratio is reduced to 50% or less so that lactic acid formation increases upon oxygen deliveries that would normally be sufficient to meet aerobic oxygen demand.[23] A further explanation of lactic acid production in face of adequate oxygenation could be a mitochondrial dysfunction during sepsis so that anaerobic metabolism occurs and pyruvate is shunted toward lactate production.

In hemodynamically stable patients with sepsis, hyperlactatemia might be the result of impaired lactate clearance rather than overproduction, namely in patients with preexisting or new hepatic dysfunction.[24] The concept of lactate clearance was convincingly underlined by Nguyen *et al.*,[25] however, to date a full consensus does not exist about its prognostic value of outcome in septic patients.[26,27]

Lactate clearance could be considered an alternative target to central venous saturation in determining whether oxygen delivery is adequate during septic shock resuscitation. In fact, an important and randomised study reported how a decrease in lactate concentration of more than 10% while central venous saturation was still below 70% was associated with better outcome (8% mortality) compared with central venous saturation above 70% without adequate lactate clearance (41% mortality).[28] Similarly, other Authors found that using lactate-guided therapy compared with control and found a significant reduction in hospital mortality.[29] supporting the concept that a decrease in elevated lactate concentrations might reflect successful management. In human medicine the speed at which hyperlactatemia resolves with appropriate therapy may be considered a useful prognostic indicator in critically ill, even if lactate alone should not be considered sufficient to judge success or failure of treatment.

How and when lactate should be measured

An increased anion gap can be considered as screening tool for the diagnosis of lactic acidosis, even if a normal anion gap does not completely exclude the possibility of lactic acidosis.

The correlation between venous and arterial blood lactate concentrations is significantly close allowing

to assess lactate either in venous or arterial blood sample.[30] It is important to consider the conservation of sample, which should be measured within 15 min or should be placed on ice to prevent falsely high concentrations of lactate derived from erythrocytes and leukocytes. The latest International Guidelines for Management of Severe Sepsis and Septic Shock (Surviving Sepsis Campaign) recommends measuring blood lactate within 3 h of presentation in acute care setting,[31] since blood lactate has showed to be particularly effective as a triage tool in patients with normal hemodynamic parameters.

Treatment of lactic acidosis in sepsis

Lactic acidosis is prevalently associated with tissue hypoperfusion and acute circulatory failure that should be promptly corrected with adequate liquid infusion. Moreover, treatment of lactic acidosis requires identification of the primary cause of shock and appropriately directed therapy. Since most cases of lactic acidosis depend on whole-body oxygen delivery failure, the maximization of systemic oxygen delivery remains the primary therapeutic focus. Therefore, appropriate treatment of shock, restoration of circulating fluid volume, improved cardiac function, identification of sepsis source with appropriate therapy, and resection of any potential ischemic regions, defined as early goal-directed therapy for sepsis, is well described and is associated with improved outcomes.[32] Initial resuscitation aims to correct deficits in whole-body oxygen delivery and the macrocirculation. However, effective resuscitation also requires the microcirculation to be addressed, obtaining adequate microcirculatory volume in order to recruit inadequately perfused capillary beds. Moreover, because microcirculatory abnormalities arise as part of the systemic inflammatory response of sepsis, this aspect should be improved by an adequate treatment of infection. A further important issue is the increase of lactic acid secondary to adrenergic agonists use. In fact, beta-adrenergic stimulation contributes substantially to an increased lactate production in shock states by increasing glycolytic flux.[13] As showed in the vasopressin and septic shock trial, in patients with septic shock, reduction of the norepinephrine dose by adding low-dose vasopressin improved survival by 10% in patients initially receiving less than 15 mg/min norepinephrine.[33]

When initial resuscitation does not substantially or completely correct lactic acidosis, it is also essential to consider other causes, such as regional production of lactate, possible toxin induced or bowel-associated impairment of cellular metabolism, biguanide therapy, malignancy, alcoholism, HIV medications (reverse transcriptase inhibitors), or intestinal malabsorption syndromes.

The treatment of acidosis is still debated, namely the potential use of buffering agents (specifically bicarbonate) to reverse the potentially negative effects of acidosis, however their use is generally advocated in the setting of severe acidosis. Though theoretically appealing only few studies document safety and efficacy of alkali therapy in lactic acidosis. In a RCT comparing equi-osmolar sodium bicarbonate to sodium chloride in patients with lactic acidosis, there were no hemodynamic differences between the two groups.[34] The latest International Guidelines for Management of Severe Sepsis and Septic Shock recommends against use of bicarbonate therapy for the purpose of improving hemodynamics or reducing vasopressor requirements in patients with hypoperfusion induced lactic acidemia with pH $\leq$7.15.[31] In all other circumstances, when lactic acidosis is accompanying pulmonary edema, cardiopulmonary arrest, grand mal seizures, biguanide therapy, ethanol ingestion, and diabetic ketoacidosis, bicarbonate therapy is not recommended.

The starting dose of sodium bicarbonate ($NaHCO3^-$) is one third to one half of the calculated extracellular bicarbonate ($HCO3^-$) deficit, as illustrated by the following formula:

$$HCO3^- \text{ deficit (in mEq)} = 0.5 \times (\text{Wt in kg}) \times (\text{Desired } HCO3^- - \text{Measured } HCO3^-) \quad (2)$$

Metabolic alkalosis can ensue after bicarbonate administration if the correction is complete rather than partial. Such result should be avoided by titration of the bicarbonate dose to partial therapeutic end points that could be arterial pH of 7.20. Moreover, in severe hypoxemia, sodium bicarbonate should be administered by slow infusion to minimize any increase in central venous carbon dioxide tension. Sodium bicarbonate may precipitate ventilatory failure since bicarbonate administration increased carbon dioxide (CO_2) production. Therefore, sodium bicarbonate must be given with caution and minute ventilation must be increased in order to expel a major extent of CO_2.

In patients affected by renal failure not strong evidence exists that lactic acidosis could be corrected by bicarbonate-based hemodialysis lowering lactate concentrations and normalizing pH.[35] Others factors, which could reduce lactic acidosis have less evidence and are restricted to particular circumstances. In case of thiamine deficiency, associated with lactic acidosis and cardiovascular failure, *thiamine repletion* (given as 50-100 mg intravenously followed by 50 mg/d orally for 1-2 weeks) may have dramatic and potentially lifesaving effect. *Dichloroacetate* enhances the activity of pyruvate dehydrogenase and lowers lactate concentrations when oxygen is available. Although, in a large RCT dichloroacetate reduces arterial lactate concentrations and improves acidemia, this does not

influence hemodynamic parameters or patient survival.[36] *Tris hydroxymethyl aminomethane* (THAM) is a weak alkali and theoretically has the advantage over bicarbonate as it produces less carbon dioxide, however, clinical trials do not prove THAM to be more effective than bicarbonate. *Carbicarb* is an equimolar combination of sodium carbonate and sodium bicarbonate that produces less carbon dioxide than sodium bicarbonate alone offering theoretical advantages over sodium bicarbonate.

Conclusions

Lactic acidosis is an important and frequently underdiagnosed condition in patients with severe sepsis or septic shock. It strongly correlates with tissue hypoxia even if it is advisable to consider other causes, namely when lactic acidosis does not resolve after early resuscitation and treatement of infection. The level of lactate is prognostic for illness severity and mortality of patients with sepsis. Monitoring lactate clearance is promising as an indirect measure of adaptive response to metabolic processes of severe infection and response to therapies, however, in order to use lactate clearance correctly, physicians should understand the complexity of lactate metabolism and never consider such paramenter alone but combining it with additional clinical information.[37] In the next future, ongoing research into lactate clearance, and probable noninvasive surrogate measures, may add further insight into outcome-based practices.

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