Serum lactate: role in the assessment of microhemodynamics in critically ill patients

Many critically ill patients with stabilized hemodynamics die with signs of multiorgan failure. One of the reasons is the derangement of microcirculation and tissue perfusion. It has been shown that microcirculatory distress left uncorrected for 24 hours is single independent predictor of mortality in sepsis. Serum lactate is the only indicator of microcirculatory changes that is monitored routinely in all critically ill patients. It has been widely believed that hyperlactatemia in sepsis is marker of tissue hypoxia and indicates the existence of oxygen debt resulting from tissue hypoperfusion and anaerobic glycolysis. Attempts to correct hyperlactatemia by delivering supranormal oxygen amounts have failed in septic patients. The term “shock” lactate refers to hyperlactatemia originating from oxygen debt. Human studies failed to demonstrate the relationship between hyperlactatemia and tissue hypoperfusion in the late phase of sepsis. Adrenergic stimulation in sepsis and accelerated aerobic glycolysis have been proposed as a likely mechanism of hyperlactatemia. Both exogenous and endogenous catecholamines are correlated with septic hyperlactatemia. Aerobically generated lactate mediated by cytokines is called “stress” lactate and may serve as a marker of hypermetabolism rather than tissue hyperperfusion. Many studies and guidelines recommend targeting resuscitation to normalize lactate in septic patients. These recommendations need to be taken with reserve. Since lactate serves, under stress, as a source of energy and can be used as a fuel for oxidation as well as for glucose production, attempts to normalize lactate might be even harmful. Although high lactate clearance, due to a correction of oxygen debt contributes to a better prognosis in sepsis, the unusual complexity of lactate makes it almost impossible to make an unambiguous therapeutic decision, when comes to a lactate-guided treatment in sepsis.

Key words: lactate, microcirculation, sepsis, critically ill

INTRODUCTION

Despite progress that has been made in understanding hemodynamic changes during critical illness, many critically ill patients with stabilized hemodynamics die with signs of multiorgan failure. One of the reasons is derangement of microcirculation and tissue perfusion. Technical progress in past decades has enabled meticulous hemodynamic assessment, but most of monitoring systems and hemodynamic parameters focus on macrohemodynamics. However, in critical illness, a vulnerable physiologic compartment responsible for oxygen transport and cellular breathing stays hidden behind the systemic circulation. Its dysfunction is crucial for the development of organ dysfunction in critical illness.

Microcirculation is consisted of the smallest blood vessels, arterioles, capillaries and venules, all of them with diameter less than 100 μm. Their main role is to take part in oxygen and nutrients transport to tissues, to enable immunologic functions and delivery of drugs to target cells during disease states. Microcirculation is characterized with structural and functional heterogeneity in different organs and the main determinants of capillary flow are driving pressure, arteriolar tone, hemorheology and capillary patency.

Dissociation between micro- and macrohemodynamics is one of the features of sepsis. Various factors acting during critical illness, affect virtually all cellular components of microcirculation, including endothelial cells, smooth muscle cells, leukocytes, erythrocytes and tissue cells. These disturbances cause tissue respiratory distress, which might, through cascade of pathologic mechanisms lead to organ dysfunction. It has been shown that
microcirculatory distress left uncorrected for 24 hours is single independent predictor of mortality in sepsis.\(^8,9\)

Having in mind the fact that global hemodynamics doesn’t correlate with microcirculation status and that it is the first to change and last to recover during sepsis, it is obvious why monitoring of microcirculation is considered vital in septic patients.

Different techniques have been used for assessment of microcirculation in critically ill. They include methods based on clinical assessment of tissue perfusion, such as warmth of skin and capillary refill time, body temperature gradients, tissue oxygenation and capnometry.\(^10\)

Nowadays, it is possible to observe the microcirculation at the bedside with handheld microscopes. The Sidestream Dark Field (SDF), the Orthogonal Polarization Spectroscopy (OPS) or Cytocam-IDF (incident dark field illumination) are the devices that enabled clinicians the insight into sublingual microcirculation.\(^11\)

According to the report of a round-table conference, held in 2005, following parameters were suggested for evaluation and scoring of microcirculation: vessel density, proportion of perfused vessels, microcirculatory flow index and flow heterogeneity index.\(^12\) Although they give the information about the amount of perfused vessels and the quality of flow, these bedside technologies are underused in intensive care units worldwide, due to unavailability and lack of clinical studies that support microcirculation-targeted resuscitation.\(^13\)

It seems that the only means of microcirculation evaluation that has been used widely and routinely on a daily basis is monitoring of serum lactate.

**LACTATE PHYSIOLOGY**

Lactate is a phenomenal small three carbon molecule that is produced and metabolized ubiquitously, representing also, in the same way as glucose, the central substrate for energetic processes in the body. A standpoint that lactate represents just a waste product of glycolysis has been revolutionary changed since a bulk of evidence confirmed its significant cell to cell shuttle.\(^14\) It has been suggested that lactate plays and important role as an intermediary in metabolic processes and serves as a mediator in regulation of redox state in different intracellular and extracellular compartments.\(^14\)

Thus, lactate has a more complex meaning, representing at the same time the waste product of anaerobic metabolism and a fuel for aerobic processes, the signal of distress and the sign of plenty.

Lactate is produced in the cytosol during glycolytic metabolism of glucose. (Figure 1) The end product of glycolysis is pyruvate which is transferred via mitochondrial membrane and converted to Acetyl-CoA. Subsequent citric acid (Krebs) cycle and oxidative phosphorylation enable highly efficient aerobic energy production of 36 moles of ATP. Pyruvate can also be converted into lactate. This reversible process is catalysed by lactate dehydrogenase (LDH). It is important to note that anything that causes pyruvate to accumulate will cause the accumulation of lactate. It can be due to an excessive glycolysis that overwhelms the mitochondria, a blocked mitochondrial function because of hypoxia or lack of reducing agent or inflammatory mediated enzymatic dysfunction which disables pyruvate transfer to mitochondria.

Serum lactate concentration represents the balance of lactate production and consumption and it is normally less than 2 mmol/L.\(^15\)

**LACTATE AS A MARKER OF TISSUE HYPOPERFUSION**

Lactate has been widely used as a biomarker for screening, diagnosis, risk stratification and monitoring in critically ill patients.\(^15\) It has been demonstrated by multiple studies that hyperlactatemia is a reliable marker of disease severity and mortality predictor in various populations of critically ill and surgical patients.\(^16,17,18\) Even mild hyperlactatemia was associated with increased ICU and hospital mortality.\(^19\)

An elevated serum lactate has been traditionally accepted as the evidence of hypoxia and oxygen debt caused by hypoperfusion and consequent anaerobic glycolysis. This widespread viewpoint originates from pioneer researches from 1960s being the first to demonstrate the association between lactate accumulation and oxygen debt during the experimental model of haemorrhagic shock.\(^20,21\)

Delivery/consumption charts clearly show that fall of oxygen delivery (DO2) after the critical DO2 point has been reached leads to decrease of oxygen consumption. (Figure 2) Past the critical DO2 point, the tissues need more oxygen then they are getting, so anaerobic respiration and oxygen debt take place. Lactate levels are stable and low whilst there is enough oxygen, but after the critical point they rise sharply. Delivery/consumption charts lead us to conclude that high lactate must mean the existence of oxygen debt and that oxygen debt must indicate the need for higher oxygen delivery. It is the rationale that
motivated William Shoemaker to revolutionary change the approach to critically ill surgical patients, during the 1980s. His strategy of achieving “supranormal” oxygen delivery and consumption in high risk surgical patients resulted in increased survival.22 Many of those patients had the increased lactate levels which were assumed to reflect the anaerobic state. It resulted in assertion that targeting supranormal global oxygen delivery in critically ill surgical patients would positively affect the outcome.23

It is logical and maybe acceptable theory for high risk surgical patients, but when Gattinoni and Hayes applied the same “supranormal” goals to septic patients, they found the following results:24,25

1. Supranormal goals (cardiac index above 4.5 l/m² or \(S_O_2 = 70\%\)) were difficult to achieve in critically ill patients.

2. Supranormal oxygen delivery didn’t mean more survivors, it meant less.

3. Higher dobutamine doses were associated with increased mortality.

4. Supranormal hemodynamic values didn’t lower the arterial lactate levels.

The question was set: why supranormal goal directed therapy succeed in surgical patients but failed in septic patients? The answer is not simple, but the first problem might be the difficulty in finding the evidence of tissue hypoxia and tissue oxygen debt in patients with sepsis. High lactate as the evidence of anaerobic metabolism is the conclusion derived from the animal experimentation using circulatory shock as a model. But septic shock is much more complex.

An interesting observation in papers dealing with strategies to increase oxygen delivery is that what really determines survival might not be the oxygen transport itself. It is the patients who are able to increase oxygen consumption (\(VO_2\)) during critical illness, that survive.26,27

HYPERLACTATEMIA IN SEPTIC PATIENTS

The diagnosis of septic shock is based on clinical signs and laboratory parameters and among these hyperlactatemia has been promoted by the newest consensus as an important diagnostic criterion.28,29 What causes hyperlactatemia in sepsis and septic shock? It is difficult to give a simple answer.

The traditional view at raised blood lactate is that it represents the evidence of ongoing tissue hypoxia. Certainly, there are several mechanisms during the course of sepsis that may lead to the development of global oxygen debt with consequent anaerobic glycolysis and lactic acidosis. The presence of delayed or inadequate resuscitation during early sepsis results in global tissue hypoperfusion and lactate acidosis. This finding is supported by many experimental and clinical studies.30 The other important issue is change in the oxygen delivery and consumption ratio. It is reported that patients with sepsis display increased critical oxygen delivery values (\(cDO_2\)), where oxygen consumption (\(VO_2\)) becomes supply dependent at higher values of oxygen delivery (\(DO_2\)).31 Hyperlactatemia in sepsis might also be the consequence of regional oxygen debt, even with normal global markers of tissue oxygenation. Perfusion heterogeneity on micro- and macrovascular level, so typical for sepsis, can result in occult oxygen debt and anaerobic lactate production in vulnerable tissues, such as gut mucosa, despite normal \(DO_2\). Low gastric intramucosal pH in sepsis is the marker of covert splanchnic ischemia and the presentation of local oxygen debt despite normal oxygen derived measurements.32 The term “shock” lactate can be used to describe hyperlactatemia due to oxygen debt of any kind.

The problem is that in resuscitated sepsis it has been difficult to demonstrate oxygen debt at tissue level and to show the relationship between hyperlactatemia and deranged tissue oxygenation.
Mixed venous oxygen saturation (SvO₂) serves as a measure of oxygen debt in low cardiac output states and its low value indicates high oxygen extraction and global oxygen debt. It is well-known that in septic patients its values can be low, normal or even high, suggesting that oxygen utilization in sepsis plays also an important role. It is accordant with findings of Astiz who demonstrated that serum lactate and SvO₂ show no correlation in septic patients. The results of large randomized trials in diverse populations of intensive care patients have shown no benefit on survival in attaining high levels of oxygen delivery. In Hayes study there was no difference in serum lactate levels between the high DO₂ group and the control throughout the study period. It cannot be stated that it was because it wasn’t possible to prove the existence of oxygen debt in the intervention group or because the patients were unable to extract or use the available oxygen. It appears that macrohemdynamic optimization guided by dynamic or static variables doesn’t guarantee an adequate tissue perfusion and cellular respiration. Loss of hemodynamic coherence is one of the most prominent features of sepsis. Sepsis induces flow abnormalities which have been demonstrated at all vascular levels. The cellular effects of changes in microcirculatory flow are mostly unknown, but the majority of available data does not support the hypothesis that microvascular disturbance results in tissue hypoxia. Many investigators failed to show correlation between serum lactate and surrogate markers of tissue oxygenation. Sair and coworkers measured muscle and subcutaneous pO₂ in septic patients and healthy volunteers and found an increased muscle oxygenation in septic patients despite significantly higher lactate values. The other study has also found an increased pO₂ in biceps muscle of patients with septic shock, showing that even in the most severe forms of shock, muscle oxygenation doesn’t seem to decrease.

Studies that examined surrogate markers of the adequacy of tissue oxygenation, such as intracellular ATP, phosphocreatine or inorganic phosphate, failed to demonstrate cellular hypoxia despite high serum lactate. Hypoxia-inducible factor (HIF-1α) whose production in tissues is enhanced during hypoxia, leads to the marked expression of genes that either cause an increase in oxygen delivery or decrease in oxygen consumption (like glycolytic enzyme genes). However, Regueira and colleagues didn’t demonstrate the relationship between HIF-1α production and hyperlactatemia in patients with septic shock. The fact that lungs, organ that receives the whole cardiac output, represents one of the most important sources of lactate in sepsis, indirectly confirms lack of this relationship.

It appears that tissue hypoxia is unlikely to be the main cause for hyperlactatemia in sepsis. What else could be responsible for rise of lactates in sepsis?

It is well known that inflammation and cytokine production are responsible for many metabolic changes during the course of sepsis. It has been postulated that sepsis induces an impaired activity of pyruvate dehydrogenase (PDH), enzyme responsible for conversion of pyruvate into acetyl-coenzyme A in the mitochondria. The study by Alamdari and coworkers has shown that inhibition of PDH complex can be noted after 24hours of sepsis. Decreased uptake and mitochondrial conversion of pyruvate lead to accumulation of lactate without any indications for cellular hypoxia.

The other possible explanation for sepsis-induced hyperlactatemia is that it comes from the adrenergic state and significant increases in cellular ATP needs. Activated leukocytes promote glycolysis to meet their increased energy needs. The paper by Hajj-Michael has clearly demonstrated that almost half of lactate production during sepsis can be attributed to leukocyte production. Sepsis induced metabolic state is followed by increased expression of membrane glucose transporters and genes of important glycolytic enzymes and it is also the supposed mechanism of lactate production through an intensified glycolysis. Protein catabolism leads to release of significant amounts of alanine which is further converted to lactate by ALT.

Adrenergic stimulation with exogenous and endogeneous catecholamines activates Na⁺/K⁺-ATPase and stimulates glicogenolysis and glycolysis. Huge amounts of pyruvate generate lactate under totally aerobic conditions. Blockade of Na⁺/ K⁺-ATPase with ouabain as demonstrated by Levy and coworkers, leads to decreased lactate production in skeletal muscles of septic patients. It is an interesting observation that beta-blockade leads to decreased lactate production despite its tendency to lower cardiac output and oxygen delivery. Wutrich et al have shown that a potential for rise of arterial lactate during an epinephrine infusion determines a better prognosis in sepsis.

Aerobically generated lactate mediated by cytokines can be called “stress lactate” to distinguish from anaerobic or “shock lactate” and may serve as a marker of hypermetabolism rather than tissue hypoperfusion.

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**TABLE 1**

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<thead>
<tr>
<th>CHARACTERISTICS OF &quot;SHOCK&quot; AND &quot;STRESS&quot; LACTATE</th>
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<tbody>
<tr>
<td>Source</td>
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<tr>
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</tr>
<tr>
<td>Muscle, Gut</td>
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<tr>
<td>Inflammatory cells, lungs</td>
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<td>DO₂ responsiveness</td>
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<tr>
<td>Tissue hypoxia</td>
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<td>Accelerated glycolysis</td>
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The role of “stress lactate” has not been thoroughly elucidated, but there are several possible explanations for this adaptive response. Lactate is a small and mobile metabolite which makes it suitable for recycling and ATP provision and at the same time buffering the protons produced during ATP degradation. In sepsis, lactate reversion to pyruvate and oxidation in the mitochondria provides energy without need for utilization of free fatty acids. Shock states are characterized by myocardial shifting from free fatty acids consumption to lactate as a dominant energy source. It supports the hypothesis that epinephrine infusion increases cardiac performance partly through the release of lactate as a fuel for myocardium in the state of shock. It should be kept in mind when applying therapeutic strategies aimed to normalize lactate in septic patients. (Table 1) (Figure 3)

In conclusion, high initial blood lactate levels are a marker of tissue hypoperfusion in patients with septic shock, expressing the need for appropriate resuscitation and monitoring. In haemodynamically stable patients without clinical evidence of shock, hyperlactataemia may represent hypermetabolism, mitochondrial dysfunction or alterations in production and clearance rather than cellular hypoxia.

The interpretation of an elevated serum lactate in septic patients remains a complex issue. The different origins and purpose of “shock lactate” and “stress lactate”, varying at different times in their relative contribution to the hyperlactatemia of sepsis makes it quite difficult to make an unambiguous decision regarding lactate-guided therapeutic algorithms in septic patients.

**SUMMARY**

**SERUMSKI LAKTAT: ULOGA U PROCENI MIKROHEMIDONAMIKE KOD KRITIČNO OBOLELIH**

Mnogi kritično oboleli pacijenti nakon stabilizovanja hemodinamike umiru sa znacima multiorganске disfunkcije a jedan od razloga je poremećaj mikrocirkulacije i tkivne perfuzije. Pоказано je da je nekorigovan mikrocirkulatorni distres nezavisni prediktor mortaliteta u sepsi. Serumski laktat je jedini pokazatelj mikrocirkulatornih promena koji se rutinski prati kod svih kritično obolelih pacijenata. Široko je rasprostranjeno stanovište da je hiperlaktatemia u sepsis marker tkivne hipoksije i da ukazuje na postojanje kiseoničnog duga nastalog zbog tkivne hipoperfuzije i anaerobne glikolize. Pokušaji da se hiperlaktatemia koriguje isporukom supranormalnih količina kiseonika nisu dali rezultata kod septičnih bolesnika. Termin “laktat šoka” odnosi se na hiperlaktatemiiju koja je posledica kiseoničnog duga. Mnoge studije nisu uspele da prikažu povezanost hiperlaktatemije i tkivne hipoperfuzije u kasnim fazama seps. Adrenergička stimulacija u sepsi i ubrzana aerobna glikoliza smatraju se mogućim mehanizmima hiperlaktatemije, pri čemu i egzogeni i endogeni kateholaminii koreliraju dobro sa septičnom hiperlaktatemijom. Aerobno stvoreni laktat pod dejstvom citokinova naziva se laktatom “stresa” i pre je pokazatelj hipermetabolizma nego hipoperfuzije. Mnogi vodiči preporučuju ciljana terapiju usmerenu na normalizaciju laktata kod septičnih bolesnika. Ovakve preporuke treba uzeti sa rezervom.

Kako laktat u uslovima stresa služi kao izvor energije i može se koristiti kao supstrat za oksidaciju ali i produkciju glukoze, pokušajte da se serumski laktat normalizuje možu čak biti štetni. Iako visok laktatni klirenz zbog korekcije kiseoničnog duga doprinosi boljoj prognosti u sepsi, izrazita kompleksnost laktata čini govo nemogućim donošenje nedvosmislenih terapske odluke kada je u pitanju laktatom-ciljana terapija kod septičnih bolesnika.

Ključne reči: laktat, mikrocirkulacija, sepsa, kritično oboleli

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