Section A-Research paper

An Insight about Lactate, Shock index and Sepsis

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Article History: Received 10th June, Accepted 5th July, published online 10th July 2023

Abstract

Severe sepsis and septic shock are a major health problem worldwide and among critically ill patients in particular. Beyond the identification of the likely focus of infection and of the organisms responsible, treatment with appropriate antibiotics, and drainage of the focus itself, when possible, early, and aggressive hemodynamic resuscitation is recommended for the treatment of septic patients. The identification of severe sepsis is based on clinical signs but also on laboratory findings. Among these, sepsis-associated hyperlactatemia (SAHL) has been recently promoted as a way of identifying patients with `cryptic' shock who require focused, early goal-directed therapy. The physiologic source of lactate production during sepsis is now a matter of research. Recent data indicate that other potential non-hypoxic reasons can lead to SAHL. Human studies have did not succeed to exhibit a correlation between hyperlactatemia and any markers of tissue hypoxia or other indices of reduced cellular oxygenation. If insufficient perfusion/oxygenation was the reason of hyperlactatemia, methods to increase systemic or local oxygen supply to supranormal values should correct hyperlactatemia. Conclusively, if, as seems from previous observations, SAHL is not a result of low oxygen, another justification is needed.

Keywords: Lactate, sepsis, septic shock

Introduction

Severe sepsis and septic shock are a major health problem worldwide and among critically ill patients in particular. Beyond the identification of the likely focus of infection and of the organisms responsible, treatment with appropriate antibiotics, and drainage of the focus itself, when possible, early, and aggressive hemodynamic resuscitation is recommended for the treatment of septic patients ***(Vincent, 2021).***

The identification of severe sepsis is based on clinical signs but also on laboratory findings. Among these, sepsis-associated hyperlactatemia (SAHL) has been recently promoted as a way of identifying patients with `cryptic' shock who require focused, early goal-directed therapy ***(Schlapbach, 2017).***

In fact, SAHL is a common finding, reaching levels as high as 15.0 mmol/L in some patients. Plasma lactate levels and their trend over time are reliable markers of illness severity and mortality, being recently included in a multibiomarker-based outcome risk model for adult patients with septic shock. Even relative hyperlactatemia (blood lactate concentrations >0.75 mmol/L) is independently associated with increased hospital mortality ***(Alam, 2021).***

Raised blood lactate concentrations in the setting of sepsis are frequently viewed as evidence of tissue hypoxia and/or oxygen debt secondary to hypoperfusion. According to such paradigms, SAHL is due to anaerobic glycolysis induced by tissue hypoxia. Such tissue hypoxia in widely believed to be a major cause of organ failure and mortality ***(Lestari, 2021).***

Moreover, changes in lactate concentration over time during intervention (for example, incorrectly labeled lactate `clearance') have been proposed as end points in sepsis resuscitation, as means of

determining the adequacy of oxygen delivery, and as indicators of resolution of global tissue hypoxia ***(Zanak et al., 2022).***

Despite such strongly and widely held views, the source, biochemistry, removal, and metabolic functions of lactate in sepsis remain unclear. It is also uncertain whether SAHL represents a maladaptive or protective response. The sheer complexity of lactate, a ubiquitously produced and utilized metabolite that, like glucose, is central to almost every energy-related pathway in humans, is one of the main reasons for the lack of a clear understanding of its pathophysiology and clinical meaning. ***(Marinova, 2022).***

Normal lactate metabolism:

Production:

Using carbon isotopes, production of daily lactate in resting humans is about 20 mmol/kg/day (range of 0.9 to 1.0 mmol/kg/hour). Lactate is released into the blood by different cells; however, the particular lactate balance (production minus utilization) at rest for each organ or tissue is unclear ***(Horvat et al., 2021).***

Lactate clearance is assessed at an extraordinary value of 800 to 1,800 ml/minute by examining the disposal of infused sodium L-lactate. This indicates that all the blood may be cleared of lactate every three to four minutes and that, at a concentration of 1 to 2 mmol/L, 60 to 120 mmol of lactate are removed each hour ***(Alam, 2021).***

Lactate is developed from pyruvate in the cytosol during glycolysis. Its concentration is in balance with pyruvate as preserved by lactate dehydrogenase (LDH), an enzyme that prefers lactate production and normally keeps a persistent lactate to pyruvate ratio of approximately 10:1 ***(Vincent, 2021).***

Reasonably, any cause that increases pyruvate production will encourage lactate generation. Essentially, lactate production from pyruvate creates NAD+, a main acceptor of electrons in glycolysis process; thus, enabling glycolytic energy production. Without recycling NAD+ from NADH, glycolysis cannot happen ***(Marinova, 2022).***

Removal:

Lactate is metabolized by the liver and the kidney, by direct oxidation or as a source of glucose ***(Schlapbach, 2017).***

Gluconeogenesis:

Cori cycle (gluconeogenesis) includes lactate production by muscle or other tissues and its transformation into glucose by liver and kidney. Hepatocytes are the main site of oxidative lactate uptake, and the kidneys represent about 30% of lactate metabolism. Conversion of lactate into glucose by the kidneys accounts for 50% of overall lactate transformation to glucose ***(Horvat et al., 2021).***

Oxidation:

Lactate is not only converted into glucose via the Cori cycle, but also removed by oxidation (via pyruvate and the citric acid cycle). About half of available lactate is disposed of via oxidation at rest, and 75 to 80% during exercise. This note indicates that lactate is a bioenergetic fuel during stress and can provide both spare blood glucose utilization and additional glucose ***(Lestari, 2021).***

This oxidation process has been examined in human skeletal muscle during exercise where isotope studies prove concurrent lactate uptake and release by muscle. Hyperlactatemia triggers muscle to switch from release to uptake through oxidation. Myocyte compartmentalization (into a glycolytic and an oxidative compartment) has been suggested as a reasonable justification for such simultaneous lactate generation and use in muscle ***(Alam, 2021).***

The glycolytic compartment is linked to glycogenolysis/glycolysis and lactate release. The oxidative compartment (likely close to the mitochondria) accounts for lactate uptake/oxidation. This 'intracellular lactate shuttle' hypothesis indicates that lactate generation through glycolysis in the cytosol is in equilibrium by oxidation in the mitochondria of the same cell ***(Marinova, 2022).***

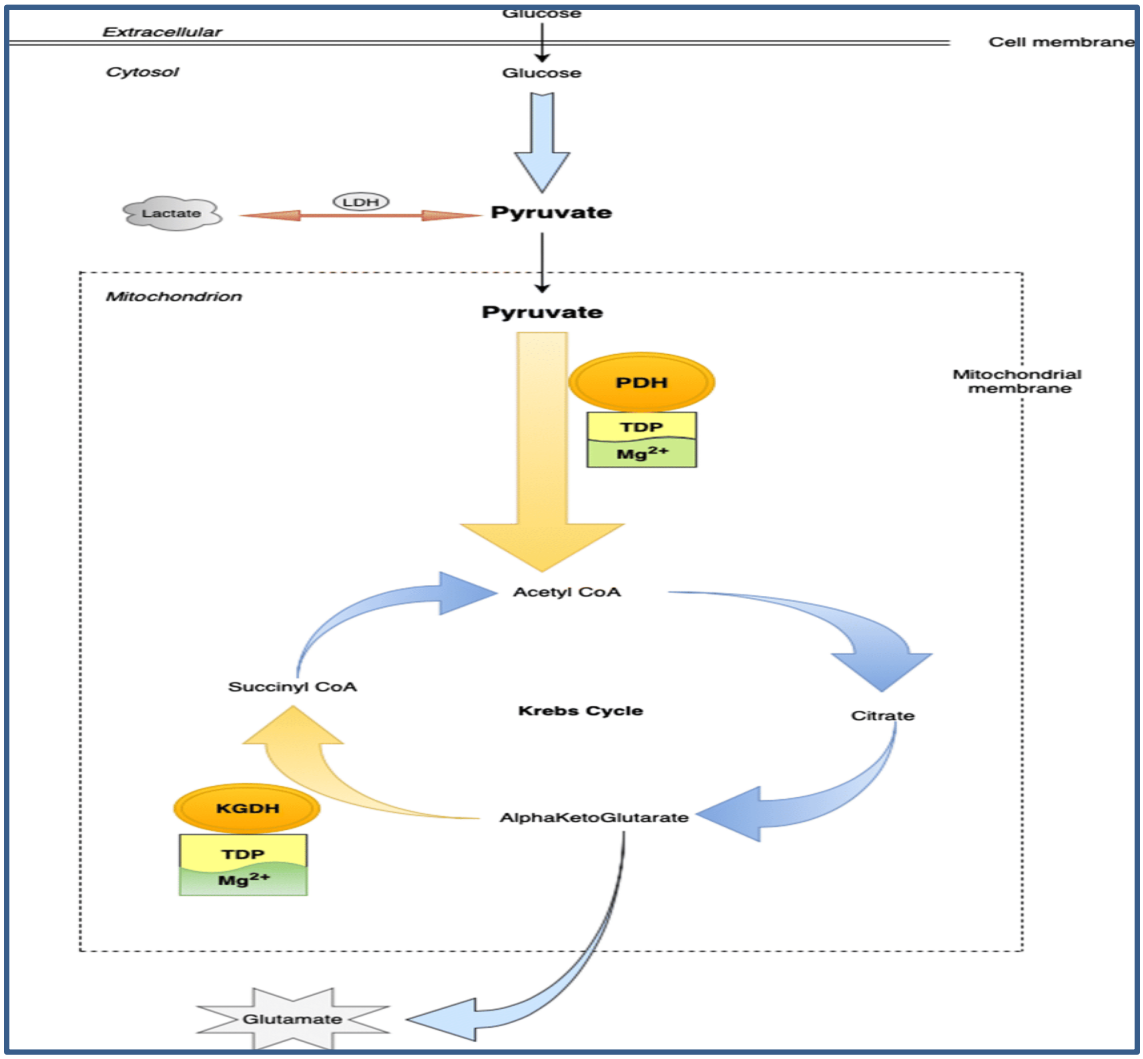

Figure (1): Normal lactate metabolism ***(Maguire et al., 2019).***

Contrarily, recent research has showed that lactate formed in the cytosol can be transferred via mitochondria by monocarboxylate transport proteins (MCTs) and oxidized to pyruvate through a mitochondrial lactate oxidation complex (mLOC). The mLOC is comprised of a mitochondrial LDH, a transmembrane glycoprotein called CD147, working as the chaperone protein for MCT type 1, and a cytochrome oxidase ***(Horvat et al., 2021).***

This complex is located in the inner membrane of mitochondria, as shown by confocal laser scanning microscopy, western blotting of cell subfractions, and immunoprecipitation techniques. Reduced concentrations of lactate in the mitochondrial matrix enable lactate mitochondrial influx and oxidation to pyruvate ***(Zanak et al., 2022).***

Pyruvate is then transferred from the intermembrane space where mLOC exists, into the mitochondrial matrix and oxidized through the tricarboxylic acid cycle. Of note, MCT1 and mLOC-related genes are differentially stimulated by lactate through a positive feedback loop ***(Vincent, 2021).***

Improving expression of lactate transporters on mitochondrial membranes permits an additional valuable 'intracellular lactate shuttle'. Some lactate can also be transferred to adjacent cells, tissues and organs to act as oxidative or gluconeogenic substrates as part of an adjacent `cell-to-cell lactate shuttle' ***(Horvat et al., 2021).***

Lactate metabolism in sepsis:

The physiologic source of lactate production during sepsis is now a matter of research. Recent data indicate that other potential non-hypoxic reasons can lead to SAHL. Human studies have did not succeed to exhibit a correlation between hyperlactatemia and any markers of tissue hypoxia or other indices of reduced cellular oxygenation ***(Schlapbach, 2017).***

Tissue hypoxia:

Previous studies calculated bicep muscle partial pressure of oxygen (PO2) by intermittent and continuous techniques in 70 patients distributed in three different groups, including sepsis, limited infection and cardiogenic shock. The authors observed normal tissue PO2 values in all groups and high rates in the septic group (reaching levels as high as 50 mmHg in the severe septic state). There was no relationship between serum lactate levels and muscle PO2 ***(Garcia, 2014).***

Even in patients in the last state of hypodynamic septic shock contributing to death, mean muscle PO2 did not decrease to <30 mmHg. Counting that normal muscle PO2 values vary from 15 to 30 mmHg, it is tough to suppose that muscle hypoxia can justify SAHL in these patients ***(Garcia, 2014).***

Mitochondrial dysfunction:

A mitochondrial defect in oxygen consumption has been proposed as an explanation for SAHL in the existence of high tissue PO2. The amount of high-energy phosphates such as ATP or phosphocreatine (PCr) and the intracellular cytosolic pH are sensitive indicators of mitochondrial function and can be used to test for such postulated bioenergetic failure ***(Alam, 2021).***

Various animal studies examined muscle metabolism in sepsis by using phosphorus 31 nuclear magnetic resonance spectroscopy. These studies did not prove any evidence of variations in high-energy phosphate metabolism (normal values of ATP were associated with lower values of PCr, which works as a reservoir for ATP). These studies showed no decrease in intracellular cytosolic pH ***(Marinova, 2022).***

Pyruvate dehydrogenase:

Mitochondrial pyruvate dehydrogenase (PDH) is an enzyme complex that adjusts the transformation of pyruvate into acetyl-coenzyme A (CoA) in the mitochondria. The function of PDH has been described to be compromised in sepsis and as another potential reason for SAHL (sepsis induced PDH impairment). Nevertheless, authors utilizing tracer methods in patients with sepsis have not noticed an insufficiency but rather an growth in PDH action and enhanced glycolytic flux to oxidation ***(Lestari, 2021).***

No reduction of muscle PDH activity was found in the initial phase of muscle lactate increases during sepsis in animals. Nevertheless, within a day, inhibition of the PDH complex occurs due to an inflammatory up-regulation of pyruvate dehydrogenase kinase (enzyme part of the PDH complex that decreases pyruvate flux through the PDH complex), consequently limiting the conversion of pyruvate into acetyl-CoA. If these changes work for humans and PDH function is reduced in sepsis, then pyruvate would accumulate. This, in turn, would increase lactate generation, with no need to invoke tissue hypoxia ***(Horvat et al., 2021).***

Further, dichloroacetate (DCA), a drug that promotes PDH complex action, reduces lactate amounts in patients with sepsis and increases the rate of pyruvate oxidation and yet has no impact on tissue PO2. Previous animal and human studies have demonstrated that DCA reduces intracellular lactate levels and has a dose-dependent hypolactatemic effect in septic cases. As DCA has no role regarding tissue oxygenation, such observations challenge the hypoxia paradigm of SAHL ***(Zanak et al., 2022).***

DO2-VO2 mismatch:

A mismatch between tissue-level oxygen delivery (DO2) and oxygen consumption (VO2) has been intended as an justification for SAHL. Thus, indicators of tissue perfusion/oxygenation (cardiac index,

DO2, VO2, oxygen extraction ratio (O2ER), central/mixed venous oxygen saturation (cSvO2/SvO2)) have been evaluated in addition to lactate blood levels ***(Vincent, 2021).***

The evidence of rising oxygen supply in patients with sepsis is based on the notion that sepsis is a hypermetabolic condition with patients having an imbalance between oxygen delivery and demand as shown by an improved lactate concentration ***(Schlapbach, 2017).***

In patients with sepsis, however, oxygen consumption and energy spending are like those of normal people, with energy expenditure essentially decreasing with more sepsis severity. Thus, there is no necessity that oxygen providing increase with sepsis. Increasing oxygen delivery in patients without an oxygen need will not improve oxygen consumption and is expected to be damaging ***(Lestari, 2021).***

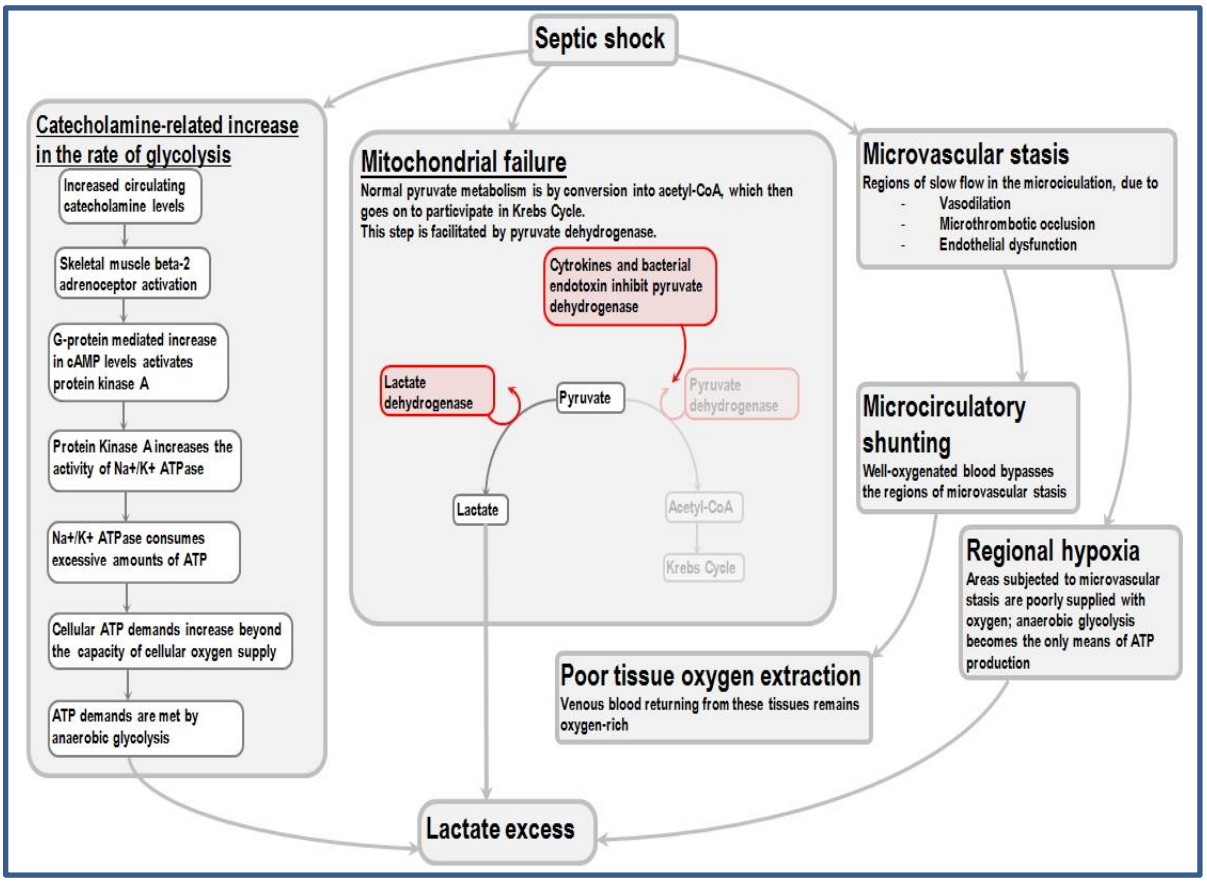

Figure (2): Lactate in sepsis ***(Alex, 2020).***

If insufficient perfusion/oxygenation was the reason of hyperlactatemia, methods to increase systemic or local oxygen supply to supranormal values should correct hyperlactatemia. Conclusively, if, as seems from previous observations, SAHL is not a result of low oxygen, another justification is needed ***(Horvat et al., 2021).***

Mechanism of hyperlactemia in sepsis and septic shock:

Adrenergic-driven aerobic glycolysis is considered the key in the process of hyperlactemia in sepsis and septic shock. Faster aerobic glycolysis induced by sepsis-associated inflammation has been suggested as a more probable justification for SAHL. In other words, SAHL provides a variation in metabolic state, not a reaction to cell oxygenation concerns. This theory maintains that a changed metabolic state happens when the rate of carbohydrate metabolism surpasses the oxidative capacity of the mitochondria ***(Marinova, 2022).***

Pyruvate is generated by an increased consumption of glucose. Pyruvate is therefore created faster than it can be converted into acetyl CoA by PDH. This raises cellular pyruvate concentration, which in turn increases lactate generation by a mass effect. This theory is simple and coherent. Though, it is vital to evaluate what observations support it ***(Alam, 2021).***

Initially, primary data gotten from whole blood mRNA analysis in patients with sepsis propose substantially increased gene expression of enzymes and membrane transporters linked to glycolytic and lactate metabolism, specifically glucose transporter (GLUT-1), hexokinase-3, pyruvate kinase (PKM-2), subunit A of LDH and MCT4 ***(Nazir et al., 2019).***

Secondary, isotope dilution procedures show that, in severe sepsis, the turnover of both glucose and lactate is boosted. Insulin resistance as seen in sepsis also enhances glycolysis and glucose-lactate cycling. Importantly, in severe sepsis, hyperlactatemia seems to be associated with increased generation whereas lactate elimination is like that of healthy subjects ***(Horvat et al., 2021).***

Pyruvate concentration is also increased by increased protein catabolism (sepsis-induced muscle proteolysis) as demonstrated by an increase in the mRNA of proteolytic genes in skeletal muscle. This can release amino acids, such as alanine, which is successively converted into pyruvate by alanine aminotransferase and afterward into lactate ***(Nazir et al., 2019).***

Endogenous/exogenous catecholamines are highly associated with hyperlactatemia in patients with sepsis. Via upregulating of their receptors, they increase the action of the Na+/K+-ATPase pump. Human and animal research found that epinephrine increases lactate creation by an increase in the Na+/K+-ATPase activity ***(Schlapbach, 2017).***

If beta-adrenergic activity accounts to a clinically related degree for SAHL then, in humans as in animal models one might assume that beta-blockade would concurrently reduce oxygen delivery and yet also reduce lactate levels. No sufficient human studies exist to confirm or disprove this consequence of the metabolic theory of SAHL ***(Zanak et al., 2022).***

Logical biochemical explanations demonstrate how adrenergic stimulation may rise lactate in sepsis. Epinephrine increases cyclic AMP, thus stimulating glycogenolysis and glycolysis with consequent creation of ATP and stimulation of the Na+/K+-ATPase pump. This activation utilizes ATP, resulting in ADP generation. ADP, via phosphofructokinase stimulation, reactivates glycolysis and therefore generates more pyruvate and, therefore, more lactate ***(Nazir et al., 2019).***

The role of Na+/K+-ATPase pump stimulation was further established by many studies when muscle lactate production was completely inhibited by ouabain. In patients with shock, the ability to increase glycolysis and lactate production upon epinephrine stimulation is linked to better prognosis, indicating that this is an adaptive reaction ***(Marinova, 2022).***

Data on the source of lactate in sepsis is lacking. This is because gaining such information would need the invasive cannulation of major veins (renal, hepatic, portal, femoral, jugular, pulmonary) in order to determine lactate fluxes across vital organs and establish whether a specific organ adds or removes lactate during sepsis ***(Nazir et al., 2019).***

Authors, using experimental cases demonstrated the lung to be the major source of lactate. The lung changed from uptake to lactate generation after initiation of endotoxemia. Muscle and liver lactate fluxes were neutral and lactate uptake occurred in the gut and kidneys before and after endotoxemia. In addition, these studies showed that lactate is carried up by both gut and kidney during sepsis to a degree that is strongly associated with organ VO2, an outcome reliable with the metabolic theory of lactate as an essential oxidation substrate during stress ***(Zanak et al., 2022).***

In patients with septic shock, the lungs are a main source of lactate like animals with a lactate generation rate of 55.4 mmol/hour. Utilizing constant infusion of isotopic lactate and pyruvate, it is supposed that the lungs concurrently extract and release lactate, and that epinephrine promotes lung conversion of pyruvate to lactate and lactate release into the systemic circulation ***(Vincent, 2021).***

Although not particularly studied in sepsis, the brain appears to be a main consumer rather than a lactate generator. As shown in critically ill patients before and after liver transplantation with or without hyperlactatemia, there is a net lactate uptake by the brain. During sepsis, the heart changes its metabolic substrate. It swings from using free fatty acids to increased lactate consumption. Therefore, the heart removes lactate ***(Alam, 2021).***

Labelled exogenous lactate studies in septic patients demonstrate that oxidation by cells is the main fate (50 to 60%) of infused lactate. This confirms the concept that hyperlactatemia signifies an adaptive

defensive mechanism by preferring lactate oxidation as an energy source. The amount of lactate not oxidized or transferred into plasma glucose, however, continues significant (about 30%) and develops a substrate for glycogen production by the liver and the kidney. Therefore, under stress, lactate works as an alternate fuel to glucose and a source of glucose itself ***(Schlapbach, 2017).***

Lactate as a prognosticator in early sepsis management:

Lactate levels on primary presentation is revealed in the most recent sepsis guidelines, with a rising result indicating tissue hypoperfusion and demanding urgent resuscitation. Even though their recommendations suggested measuring lactate soon upon presentation, many clinicians and researchers have pursued to capitalise on the test's assumed diagnostic and prognostic usage by incorporating additional readings during the resuscitation course ***(Zanak et al., 2022).***

For instance, it was revealed that lactate clearance more than 10% from primary measurement during the first 2 to 6 h of resuscitation foretold survival from septic shock and that protocols directing lactate clearance of at least 10% formed similar short-term survival percentages to protocols consuming ScvO2 checking ***(Chertoff, 2015).***

Besides, it was explained that for every 10% rise in lactate clearance, there was a corresponding 11% decline in in-hospital mortality. Comparably, patients with sepsis with lactate clearance of greater than 20% during the first 8 hours of resuscitation had a 22% reduction in the relative risk of mortality, in comparison to patients having lactate clearances of less than 20% ***(Chertoff, 2015).***

Since these primary studies are assessing lactate as a marker of recovery in sepsis and septic shock, future research has assessed the role of lactate observing during the early resuscitative period. For instance, Puskarich et al. examined resuscitation during the first 6 hours of treatment and revealed that attaining an ScvO2 goal ≥70 % without obtaining a lactate clearance goal ≥10 % was linked to greater mortality than reaching the lactate clearance goal without the ScvO2 goal ***(Puskarich et al., 2012).***

Additionally, these same investigators revealed that early lactate normalization (within 6 h) was a predictor of survival in patients being treated for sepsis and septic shock. Nguyen et al. studies the addition of lactate clearance within the initial 12 hours of resuscitation to the severe sepsis resuscitation bundle and concluded that including lactate clearance results in an almost twofold increase in relative risk reduction of death ***(Nguyen et al., 2011).***

In response to the research confirming the use of lactate clearance in early sepsis, the latest surviving sepsis guidelines for early goal-directed therapy (EGDT) contains lactate clearance during the initial 6 hours of resuscitation as an aim of primary resuscitation. Therefore, evidence regarding lactate monitoring as a marker of recovery in severe sepsis and septic shock has demonstrated successful but has primarily concentrated on the early resuscitation period ***(Chertoff, 2015).***

Lactate as a late prognosticator in sepsis management:

Previous research evaluating the clinical and prognostic use of lactate measures in the medical management of sepsis beyond the initial 6-h resuscitation phase is significantly less vigorous. Several studies have observed that increased initial and 24-hour lactate levels are important predictors of death. In addition, they realized that lactate clearance assessed 24 hours after admission was a significant predictor of in-hospital death, and that the duration of persistent lactic acidosis predicted mortality more accurately than the primary lactate value ***(Vincent, 2021).***

Comparably, many studies demonstrated that survivors of severe sepsis admitted to the medical intensive care unit had significantly lower lactate values at 24 h of resuscitation than nonsurvivors. They also showed serial lactate measurements and the duration of hyperlactemia to be consistent indicators of morbidity and mortality after trauma ***(Chertoff, 2015).***

Lactate clearance in management of sepsis:

Several authors demonstrated that 'lactate clearance', known as the reduction percentage of lactate from emergency department presentation to 6 hours later, was an important predictor of mortality. They showed that 'lactate clearance in the initial hospital course may suggest a determination of global tissue hypoxia and that this is linked to decreased mortality rates.' ***(Garcia, 2014).***

Dellinger et al. expanded the notion of targeting resuscitation in sepsis to achieve a lactate `clearance' of at least 10% as a predictor of restoration of oxygen delivery to the tissues with resuscitation treatment. Nevertheless, they require evidence to explain any assumption that this fall is due to a correction of an oxygen balance. The latest Surviving Sepsis Campaign guidelines advise 'targeting resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion' (grade 2C) ***(Dellinger, 2012).***

The concept of 'lactate clearance' is confusing and should not be rationally used in patients with sepsis as either the final decision point in the resuscitation strategy to control adequacy of oxygen delivery or a target for interventions (additional management to normalize lactate clearance). Additionally, the term `clearance' related to lactate is scientifically and pharmacokinetically wrong ***(Alam, 2021).***

Furthermore, high lactate generation can remain masked by increased use in patients with sepsis, indicating that a normal blood level of lactate does not confirm that its metabolism is normal. The claim favoring tissue hypoxia as the reason of sepsis-related hyperlactatemia. Yet, much evidence also confirms the point that tissue hypoxia may happen in many patients with sepsis and be a main trigger for SAHL ***(Zanak et al., 2022).***

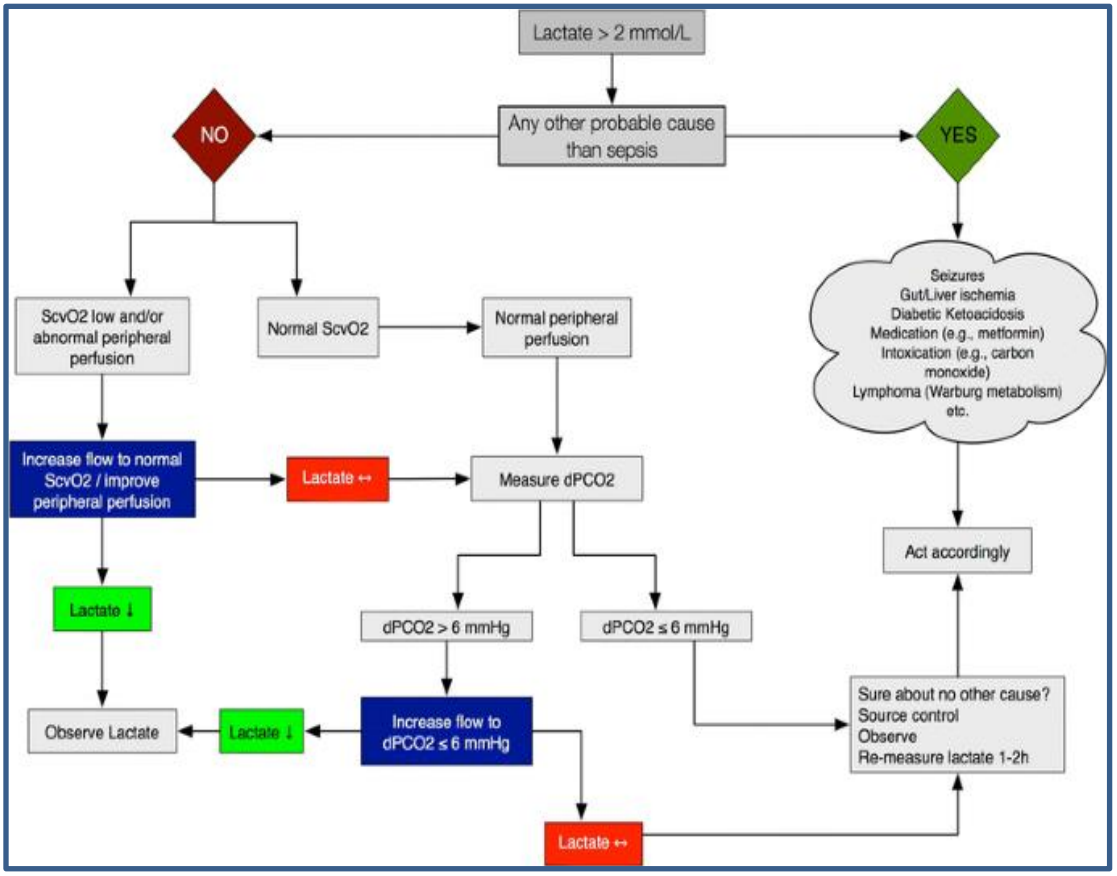

Figure (3): The clinical use of increased lactate levels. ScvO2 central venous haemoglobin oxygenation, dPCO2 central venous–arterial PCO2 difference ***(Hernandez, 2019).***

Primarily, many experimental and human studies link measures of oxygen delivery and oxygen consumption to hyperlactatemia. Such studies make a strong incidental case for lactate as a marker of dysoxia. Secondarily, studies measuring the lactate/pyruvate ratio in sepsis have proven this to be increased. Such an increased ratio offers further evidence that tissue hypoxia may occur and may be relatively frequent in the setting of SAHL ***(Lestari, 2021).***

Thirdly, latest work has emphasized the significance of the microcirculation in sepsis. Those studies show intense derangements of the microcirculation in sepsis with areas of no flow or slow flow or overly fast flow ***(Vincent, 2021).***

Such abnormalities of micro-regional flow can be seen as possible to impair oxygen delivery at a cellular level. Truly, oxygen desaturation at a venular level is found under these circumstances. Therefore, the tissue hypoxia theory offers a strong case, similar in strength to the metabolic theory presented above ***(Horvat et al., 2021).***

Shock index in sepsis:

The shock index (SI) is a bedside evaluation defined as heart rate divided by systolic blood pressure, with a normal range of 0.5 to 0.7 in healthy persons. Many investigators launched the concept as a simple and effective methods of gauging the degree of hypovolemia in hemorrhagic and infectious shock states ***(Gupta, 2020).***

Experimental and clinical studies have demonstrated that SI is linearly contrarywise associated with physiologic parameters, such as cardiac index, stroke volume, left ventricular stroke work, and mean arterial pressure. A SI $\geq$ 1.0 has been linked to significantly worst outcomes in patients with acute circulatory failure ***(Lopez et al., 2018).***

Likewise, SI was also proven to suggest constant failure of left ventricular function during forceful therapy of patients with shock in the emergency departments. Many studies expected higher illness priority at triage, more hospital admission rates, in addition to intensive therapy on admission than pulse or blood pressure alone. This indicates that SI may be a helpful method for the early detection and assessment of critical illness in the emergency department, as well to track progress of resuscitation ***(Koch et al., 2019).***

As an assistant to recognized methods, SI may detect and risk-stratify septic patients early in the emergency department course. One of these well-known markers for sepsis severity – hyperlactemia (serum lactate $\geq$ 4.0 mmol/L) - is an entry criterion for EGDT protocols and is linked to substantial short-term mortality risk ***(Gupta, 2020).***

The shock state triggers cellular hypoxia, resulting in anaerobic metabolism and higher lactate production, in addition to decreased clearance, even before vital signs are compromised. Steadily high lactate levels are linked to under-resuscitation and have been determined to down-trend with effective resuscitation ***(Lopez et al., 2018).***

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