Stress hyperlactataemia: present understanding and controversy

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An increased blood lactate concentration is common during physiological (exercise) and pathophysiological stress (stress hyperlactataemia). In disease states, there is overwhelming evidence that stress hyperlactataemia is a strong independent predictor of mortality. However, the source, biochemistry, and physiology of exercise-induced and disease-associated stress hyperlactataemia are controversial. The dominant paradigm suggests that an increased lactate concentration is secondary to anaerobic glycolysis induced by tissue hypoperfusion, hypoxia, or both. However, in the past two decades, much evidence has shown that stress hyperlactataemia is actually due to increased aerobic lactate production, with or without decreased lactate clearance. Moreover, this lactate production is associated with and is probably secondary to adrenergic stimulation. Increased lactate production seems to be an evolutionarily preserved protective mechanism, which facilitates bioenergetic efficiency in muscle and other organs and provides necessary substrate for gluconeogenesis. Finally, lactate appears to act like a hormone that modifies the expression of various proteins, which themselves increase the efficiency of energy utilisation and metabolism. Clinicians need to be aware of these advances in our understanding of stress hyperlactataemia to approach patient management according to logical principles. We discuss the new insights and controversies about stress hyperlactataemia.

Lancet Diabetes Endocrinol 2014; 2: 339–47

Published Online November 29, 2013 http://dx.doi.org/10.1016/S2213-8587(13)70154-2

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Introduction

An increased blood lactate concentration (hyperlactataemia) is typical during exercise,[1] critical illness,[2] most notably sepsis,[3] cardiogenic shock,[4] and liver failure,[5] and also during open heart surgery.[6] In almost all severe disease-related physiological stress, a raised blood lactate concentration is an independent predictor of mortality.[2,7] However, the source, biochemistry, pathophysiology, and metabolic function of lactate remain unclear. Whether such stress hyperlactataemia represents a maladaptive or protective response is also unkown.

There are many reasons for the lack of a clear understanding of stress hyperlactataemia, but perhaps the most important is the sheer complexity of lactate, a widely produced and utilised metabolite, which, like glucose, is central to almost every energy-related pathway.[8,9] Despite this extraordinary complexity, stress hyperlactataemia has been traditionally and, in our view, irrationally simplified to represent the presence of either global tissue hypoxia or tissue hypoperfusion with anaerobic glycolysis.[10] This unproven and untested basic theory has, and continues, to dominate clinical thinking and practice.[11,12]

Here, we look at key aspects of stress hyperlactataemia and explain why it cannot be used as a reliable marker of tissue hypoxia, hypoperfusion, and anaerobic glycolysis. Instead, we provide findings that show that lactate is an important aerobically produced intermediate metabolite in human bioenergetics that is oxidised as a biofuel in many different tissues including skeletal muscle, brain, heart, kidney, and liver, and that regulates the hormonal and intracellular response to stress.

Lactate metabolism

The normal value of blood lactate concentration is less than 2 mmol/L, the consequence of a balance between production and removal. Lactate can be released by many different cells.[9] Skeletal muscle,[13] adipose tissue,[14] and brain[15] seem to have a major role in lactate release, but also lung,[16] heart,[17] and gut[5] can contribute to net lactate production. The exact contribution of each tissue to net lactate production remains unknown.

Daily lactate production in resting human beings has been estimated at approximately 20 mmol/kg per day using an isotopic technique.[18] Lactate clearance calculated by the disposal of infused sodium L-lactate has been estimated to be between 800 and 1800 mL/min.[19] Lactate released into the bloodstream is transported to the liver and the kidney where it is subsequently metabolised. The internal cycling with production by tissues and metabolism by liver and kidney is known as the Cori cycle.[20]

Although hepatocytes are the main site for the Cori cycle, the kidneys account for roughly 30% of lactate metabolism.[21] Findings from studies of isotope labelled lactate in animals and in isolated human kidney tubules confirm that the renal cortex is the main lactate-consuming tissue (second to the liver) via gluconeogenesis or complete oxidation.[22–24] Nephrectomy increases the half-life of lactate elimination and decreases clearance. Renal excretion accounts for less than 1·2% of the infused load, but can increase with marked hyperlactataemia.[22,23] Renal glucose release from lactate is equivalent to 50% of overall lactate conversion to glucose.[25] Unlike the liver, the kidney's ability to remove lactate is increased by acidosis.[21]

Lactate production

Lactate formation is believed to arise from pyruvate in the cytosol as part of glycolysis. Lactate concentration is in equilibrium with pyruvate. This equilibrium is maintained by lactate dehydrogenase with a fairly constant lactate to pyruvate ratio of 10:1.[26] Thus, cytosolic lactate needs to, by enzymatic equilibrium, increase under most if not all circumstances in which cytosolic

pyruvate increases. Therefore, lactate accumulation might not imply a state of anaerobic glycolysis but simply a state of accelerated glycolysis (glycolytic flux is higher than the tricarboxylic acid cycle flux) or of decreased pyruvate dehydrogenase activity with pyruvate accumulation.

From a bioenergetic point of view, if increased glycolysis is needed to obtain more energy, a sufficient supply of NAD^+ is needed to accept electrons during its first oxidation step. This process cannot happen without an efficient mechanism in the cytosol to recycle NAD^+ from NADH. An efficient biochemical way to supply more NAD^+ is to transfer electrons from NADH to pyruvate to form lactate. Lactate dehydrogenase is the tetrameric enzyme responsible for lactate generation with five different isoforms (LDH1 to LDH5) all favouring lactate production. Compartmentalisation and the association of lactate dehydrogenase within specific organelles are believed to play a part in determining the lactate and pyruvate concentrations in each intracellular compartment. Lactate dehydrogenase is localised in the cytosol of all types of cells, and exists in high concentration in muscle, the liver, and heart.[27,28]

Lactate oxidation

Gluconeogenesis via the Cori cycle is not the only metabolic pathway for lactate utilisation. Findings of studies of radiolabelled lactate have shown that oxidation (via pyruvate and the tricarboxylic acid cycle) is another major metabolic fate for lactate.[29] Approximately half of available lactate is disposed of via oxidation at rest, and 75–80% during exercise.[30] This oxidation pathway has been assessed in exercising human skeletal muscle, in which results of isotope studies confirm simultaneous lactate uptake and release.[28,31] In fact, during exercise-induced hyperlactataemia, the active leg consumes more lactate than does the resting leg.[32] Myocyte compartmentalisation (glycolytic and oxidative compartments) has been proposed as the most logical explanation for such unexplained simultaneous lactate production and utilisation in muscle.[28] The glycolytic compartment close to the myofibrils and their glycogen stores is believed to be associated with glycogenolysis, glycolysis, and lactate release. The oxidative compartment in close proximity to the mitochondria is deemed responsible for lactate oxidation. This intracellular lactate shuttle hypothesis holds that, similar to the whole body lactate shuttle, lactate produced as the result of glycogenolysis and

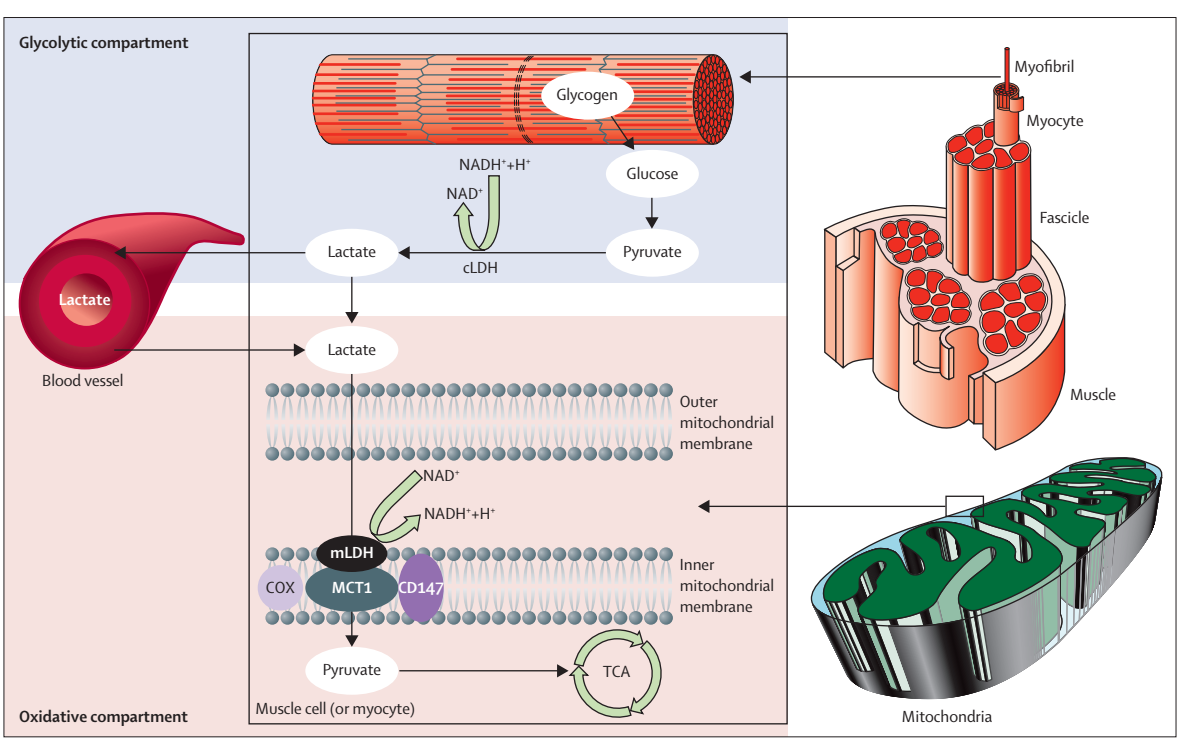

***Figure 1*: Intracellular lactate shuttle and lactate oxidation complex**
The myocyte has a glycolytic and an oxidative compartment. The glycolytic compartment in the cytosol is close to the myofibrils and their glycogen stores. This compartment is associated with glycogenolysis, glycolysis, and lactate release into the circulation. The oxidative compartment (closely associated with the mitochondria) is believed to be responsible for lactate oxidation. Lactate produced in the cytosol is also oxidised to pyruvate via the lactate oxidation complex in the mitochondria of the same cell. Pyruvate is then transported across the inner mitochondrial membrane via a monocarboxylate transport protein (MCT1). MCT1 is found in the mitochondrial inner membrane as part of the lactate oxidation complex together with its chaperone protein CD147, cytochrome oxidase, and mitochondrial lactate dehydrogenase (mLDH). mLDH is found in the outer side of the inner membrane. After pyruvate enters the mitochondrial matrix, it is metabolised by the tricarboxylic acid cycle. TCA=tricarboxylic acid cycle. cLDH=cytosolic lactate dehydrogenase.

glycolysis in the cytosol is balanced by oxidation in the mitochondria of the same cell (figure 1).[33]

Lactate produced in the cytosol is transported across lipid membranes by a family of monocarboxylate transport proteins (MCTs), is converted to pyruvate within mitochondria by mitochondrial lactate dehydrogenase, and is then oxidised as demonstrated using gold particle immunolabelling and electron microscopy.[33–35] Thus, a mitochondrial lactate oxidation complex consumes lactate in muscle at the level of the mitochondrial inner membrane as shown by confocal laser scanning microscopy, western blotting of cell subfractions, and immunoprecipitation techniques.[33] According to this model, low concentrations of lactate in the mitochondrial matrix facilitate lactate mitochondrial influx and oxidation to pyruvate. Pyruvate then leaves the intermembrane space where it is formed and transported through MCT1 to the mitochondrial matrix for subsequent oxidative catabolism via the tricarboxylic acid cycle.[8,33,34] Hashimoto and colleagues[36] found that MCT1 and related genes are differentially upregulated by lactate. Thus, lactate has a signalling role as a pseudo-hormone or lactormone that upregulates total mitochondria mass and the abundance of the mitochondrial lactate oxidation complex. This complex is composed of a transmembrane glycoptrotein CD147, which is regarded as the chaperone protein for MCT1 and cytochrome oxidase and mitochondrial lactate dehydrogenase (figure 1).[34,36] Increasing expression of lactate transporters on mitochondrial membranes allows a more effective intracellular lactate shuttle.[8,37]

Not all lactate produced in muscle is disposed by oxidation within the same cell. Some lactate is exported to adjacent cells, tissues, and organs for use as part of the cell-to-cell lactate shuttle.[34] This shuttle hypothesis states that lactate supplied from the interstitium and vasculature can be taken up and used in highly oxidative cells (eg, red skeletal muscle cells, cardiac myocytes, hepatocytes, and neurons) to serve as oxidative or gluconeogenic substrate (figure 2). The first recognised cell-to-cell lactate shuttle is the Cori cycle.[8]

The human brain changes from a net lactate producer to a lactate consumer during increased metabolic demand, using lactate as an energy substrate.[15] Blood lactate is taken up and subsequently oxidised by neurons in the conscious healthy human brain or converted to glycogen in astrocytes. The contribution of lactate as a brain energy source increases under conditions of increased lactate concentrations.[15,38] Moreover, lactate accounts for about 7% of cerebral energy requirement under basal conditions and up to 25% during exercise.[9] In an animal study in which investigators used voltage-sensitive dye, radiotracers, and sensory stimulation, lactate was used as a primary energy source during severe insulin-induced hypoglycaemia, and was readily oxidised by the brain in an activity-dependent way.[39] Collective evidence from scientific literature on brain-functional imaging supports the existence of an astrocyte-neuronal lactate shuttle in which lactate derived from astrocyte glycolysis is transported to adjacent neurons, converted to pyruvate, and oxidised via the tricarboxylic acid cycle (figure 3).[40]

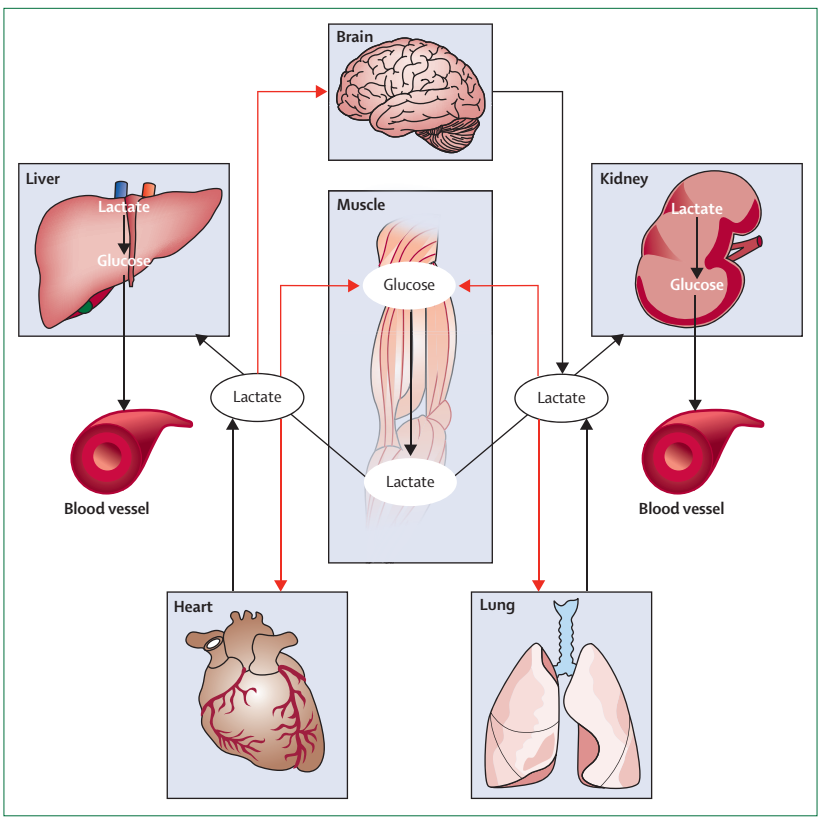

Figure 2: **Cell-to-cell lactate shuttle**
The cell-to-cell lactate shuttle hypothesis supports the idea that lactate is not only produced in muscle and disposal within the same myocyte but it can also serve as a substrate in highly oxidative cells (eg, heart and brain) or contribute to gluconeogenesis (in the liver and kidney). Lactate is also released by brain, lung, and heart.

Findings of several studies have supported the view that the heart shows net lactate uptake and oxidation at rest.[41] In a normal heart at rest, about 60–90% of ATP comes from β-oxidation of fatty acids and 10–40% comes from pyruvate formed by glycolysis and the conversion of lactate.[42] Although fatty acids have a higher yield of ATP per molecule, they have lower production efficiency.[43] Additionally, increased intracellular free fatty acids activate uncoupling proteins, allowing protons to leak into the mitochondria without generating ATP.[44] An increase in mechanical efficiency of the left ventricle was recorded when β-oxidation was inhibited.[45]

Lactate is also an important fuel for the stressed heart. The proportion of lactate uptake by the myocardium and its use as a metabolic fuel increases during exercise, β-adrenergic stimulation, increased afterload, fast pacing, and shock.[46–48] Lactate might account for up to 60% of cardiac oxidative substrate and could exceed glucose as a source of pyruvate in the presence of increased lactate concentrations.[46,47,49] During shock, the heart undergoes a major shift in substrate utilisation such that it oxidises

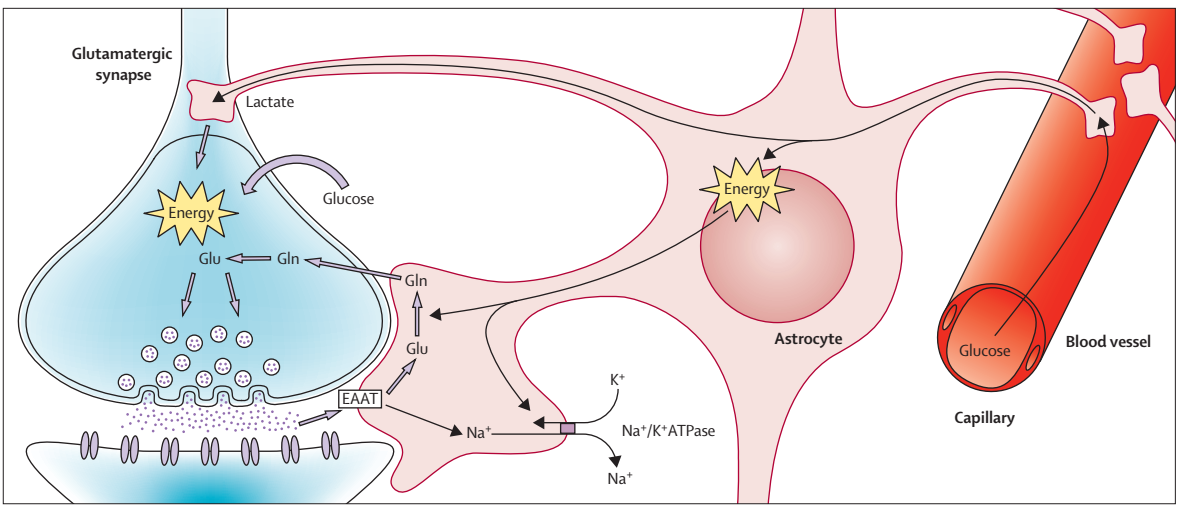

Figure 3: **Astrocyte-neuronal lactate shuttle**
Increased neuronal activity leads to glutamate release (excitatory neurotransmitter). Glutamate uptake by the astrocyte stimulates Na^+/K^+ ATPase and glycolysis with lactate production. This lactate (produced by astrocyte glycolysis or transported from blood) is taken up by adjacent neurons and oxidised via the tricarboxylic acid cycle to support neuronal energy demand. In the same astrocyte, lactate energy is used to convert glutamate to glutamine and to further sustain Na^+/K^+ ATPase function. Reproduced from Magistretti,[40] by permission of The Company of Biologists Limited. Glu=glutamate. Gln=glutamine.

lactate for most of its energy needs.[48] Therefore, accelerated lactate removal could compromise cardiac performance during shock.[50] Indeed, systemic lactate deprivation is associated with cardiovascular collapse and early death of laboratory animals;[51] lactate infusion increases cardiac output in anaesthetised pigs[52] and increases cardiac performance in patients with both cardiogenic and septic shock.[4] Data from these studies suggest that lactate is an important energy source during acute haemodynamic stress and might be an important survival response.

Hyperlactataemia during the physiological stress of exercise

There is incontrovertible evidence that moderate to high intensity exercise induces stress hyperlactataemia.[1,30,32] Many studies in which investigators used isotopes, kinetics assessment, and biopsy fluorometric assays, have shown that muscle and blood lactate accumulation increases slowly with small increments in exercise intensity. However, when a given percentage of maximum oxygen consumption ($\%VO_{2max}$) is reached, blood lactate accumulation accelerates. This inflection point has been termed the lactate threshold.[53]

During continuing exercise, the increase in lactate disposal lags behind the increase in appearance resulting in hyperlactataemia.[30] Initially, investigators considered tissue hypoxia as the cause of lactate production.[54,55] However, such studies did not measure tissue oxygen tension or use lactate tracers. Findings of many studies (table 1) now confirm that exercise hyperlactataemia is not due to hypoxia.[56–58] For example, in an animal study, Connet and colleagues[56] used myoglobin cryomicrospectroscopy techniques to determine tissue oxygen tension in the gracilis muscle contracting in situ. The researchers were unable to detect any hypoxia even during heavy workloads. Despite normal tissue oxygenation, lactate accumulation was recorded, even during mild stimulation. Pirnay and coworkers[57] found that the partial pressure of oxygen (pO_2) in femoral venous blood of human beings did not fall below the critical mitochondrial oxygen tension during maximum exercise. Richardson and colleagues[58] recorded that in six trained patients doing single-leg quadriceps exercise, intracellular pO_2 was well preserved, even at maximum exercise. Finally, under conditions of hypoxaemia (Mount Everest), no climbers developed hyperlactataemia in arterial blood samples, despite arterial pO_2 values of below 25 mmHg.[59]

Data from several studies suggest a direct, exponential association between lactate appearance and metabolic rate.[60] Simultaneously, plasma epinephrine and norepinephrine concentrations increase exponentially in a clear association with lactate production (figure 4).[60,61] In fact, increased concentrations of circulating epinephrine stimulate muscle glycogenolysis and lactate production.[60] As confirmation, Issekutz and coworkers[62] used [U-14C] lactate and [3-3H]glucose tracers in dogs running on a treadmill, and reported a decrease in glycogenolytic rate, blood lactate concentration, and lactate appearance after β-adrenergic blockage with propranolol.

Given such extraordinary capacity to produce lactate under aerobic conditions during maximum exercise, and the association with metabolic rate, it seems both logical and likely that other forms of stress hyperlactataemia should arise under aerobic conditions.

Critical illness and hyperlactataemia

There is overwhelming evidence that critical illnesses (eg, severe sepsis and septic or cardiogenic shock) are

	Method	Study details	Findings
Connet et al[56]	Myoglobin cryomicrospectroscopy techniques	Gracilis muscle studied in dogs doing exercise	Normal muscle PO_2 during extreme exercise
Pirnary et al[57]	Analysis of femoral venous blood gases from to measure oxygen consumption	Leg muscles studied in individuals doing strenuous exercise	Venous PO_2 did not fall below critical mitochondrial PO_2 during exercise
Richardson et al[58]	Phosphorus magnetic resonance spectroscopy	Individuals doing single-leg quadriceps exercise	Muscle PO_2 well preserved in normoxic conditions (FiO_2 21%)
Grocott et al[59]	Analysis of blood arterial gases	Climbers in Mount Everest	Severe hypoxaemia not associated with hyperlactataemia
Messonnier et al[60] Mazzeo et al[61]	Analysis of plasma catecholamines	Individuals doing graded exercise (trained and untrained)	Increased plasma catecholamine concentrations during exercise directly associated with an increased plasma lactate concentration
Issekutz[62]	Isotope tracers; β-adrenergic blockage (propranolol)	Dogs running on a treadmill	Decrease in glycogenolytic rate, blood lactate concentration, and lactate appearance after β-adrenergic blockage with propranolol

PO2=partial pressure of oxygen. FiO2=fraction of inspired oxygen.

Table 1: **Evidence that hyperlactataemia in exercise is not due to hypoxia**

associated with hyperlactataemia. During severe sepsis and septic shock, hyperlactataemia can reach levels as high as 15·0 mmol/L.[63] The higher the lactate concentrations are in blood, the greater is the risk of death.[64] Even relative hyperlactataemia (blood lactate concentrations >0·75 mmol/L) is independently associated with increased hospital mortality.[2]

Despite these insights from exercise physiology and molecular biology, the main basic theory is still that hyperlactataemia of critical illness is a marker of tissue hypoperfusion or tissue hypoxia, and is indicative of the onset of anaerobic glycolysis.[11,12] However, findings of studies in human beings have repeatedly failed to show an association between hyperlactataemia and any indicators of perfusion or oxygenation (oxygen consumption or oxygen delivery) or of intracellular hypoxia (table 2).

For example, Ronco and colleagues[65] tried to establish the critical oxygen delivery (DO_2) for anaerobic metabolism in critically ill patients as they approached death. An increased arterial lactate concentration was not associated with an increased critical DO_2 or impaired tissue oxygen extraction. Additionally, no difference was recorded in critical DO_2 between patients who had normal or increased arterial lactate values. Regueira and coworkers[66] measured tissue oxygenation during septic hyperlactataemia, cardiogenic shock, and hypoxaemia and found that systemic and hepatic oxygen consumption were well maintained, respiration of skeletal muscle and liver-isolated mitochondria were normal, and hypoxia-inducible factor 1α (HIF-1α) was not expressed in the skeletal and cardiac muscle, pancreas, lung, or kidney. Opdam and coworkers[67] reported substantial lactate release from the lungs of patients with shock and in patients after cardiopulmonary bypass. It is biologically implausible that the lungs, bathed in oxygen and receiving the full cardiac output, would have hypoperfusion, tissue hypoxia, or anaerobic metabolism. In fact, perfused rat lungs produce lactate under fully aerobic conditions. In a recent study,[73] investigators used continuous infusion of isotopic lactate, and reported that lungs simultaneously extract and release lactate, and that epinephrine stimulates lung conversion of pyruvate to lactate and lactate release into the systemic circulation.

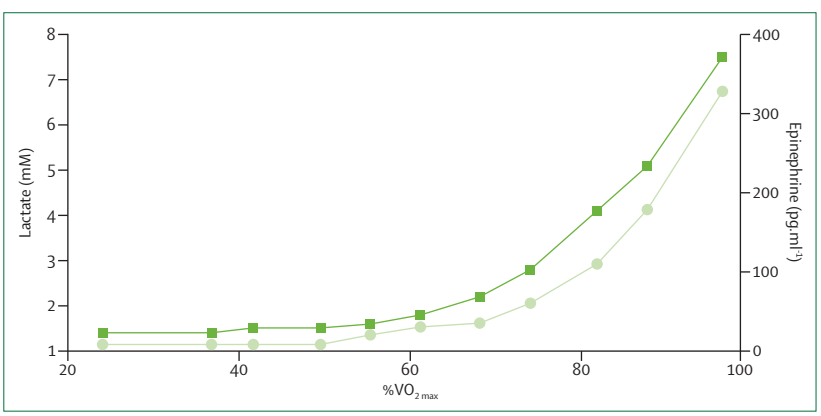

Figure 4: **Association between plasma lactate levels and catecholamine response to exercise**
Lactate and plasma epinephrine increase exponentially as a function of metabolic rate during exercise expressed as $\%VO_{2max}$. A linear relation is evident between blood lactate concentration (squares) and plasma epinephrine concentration (circles) during graded exercise. Data from references 60 and 61.

Levy and colleagues[68] measured muscle tissue pO_2 in patients with sepsis. Investigators reported value greater than 36 mmHg in all patients. Normal values at rest vary from 15 to 30 mm Hg. Boekstegers and coworkers[69] measured skeletal muscle pO_2 in patients with septic shock and found it to be abnormally high. In patients with subarachnoid haemorrhage, brain lactate metabolism and brain oxygen were measured with cerebral microdialysis. Investigators discovered that hyperlactataemia was caused by hyperglycolysis rather than hypoxia, suggesting that lactate might be used as a substrate by the injured brain.[74] Additionally, lactate is lowered by dichloroacetate, a compound that stimulates the mitochondrial pyruvate dehydrogenase enzyme complex and increases the conversion of pyruvate into acetyl-CoA, but has no effect on tissue oxygenation. Findings of several animal models and studies in human beings have shown that dichloroacetate decreases

	Method	Study details	Findings
Levy et al[51]	Microdialysis technique; selective β2-blocker (ICI-1118551) infusion; dichloroacetate infusion	Lethal model of endotoxic shock in rats	Decreased concentrations of plasma lactate, muscle microdialysate lactate, and pyruvate
Ronco et al[65]	Measurement of DO_2 and plasma lactate concentration	Critically ill patients after withdrawal of life support	No association between critical oxygen delivery and lactate concentration
Regueira et al[66]	Mitochondrial function analysis (muscle and liver biopsies); blood samples from pulmonary and carotid arteries and from portal, hepatic, and mesenteric veins	Animals with peritonitis, cardiac tamponade, hypoxic hypoxia, and controls	Systemic and hepatic consumption properly preserved; normal skeletal and liver-isolated mitochondrial function; no expression of hypoxia-inducible factor 1α in skeletal and cardiac muscle, pancreas, lung, and kidney
Opdam et al[67]	Measurement of pulmonary lactate release (difference between arterial and mixed-venous lactate, multiplied by cardiac output)	Adult intensive care patients, either after cardiopulmonary bypass or with septic shock	Lactate production by the lung under fully aerobic conditions
Levy et al[68]	Licox sensor system (Integra LifeSciences, Plainsboro, NJ, USA) microdialysis technique	Skeletal muscle (quadriceps femoris muscle) of patients with septic shock	No evidence of tissue hypoxia; muscle lactate production during septic shock under totally normal muscle PO_2 values
Levy et al[68]	Microdialysis technique; Ouabain infusion (specific inhibitor of Na^+/K^+ ATPase)	Skeletal muscle (quadriceps femoris muscle) of patients with septic shock	Muscle lactate production totally inhibited by ouabain confirming a mechanism dependent on Na^+K^+ ATPase in lactate production independent of tissue hypoxia
Boekstegers et al[69]	Intermittent polarographic needle electrode; continuous polarographic catheters	Skeletal muscle (biceps muscle) of patients with septic shock	Increased skeletal muscle PO_2, actually abnormally high compared with healthy volunteers; no evidence of tissue hypoxia
James et al,[70] Levy et al,[71] Wutrich et al[72]	Microdialysis technique and plasma epinephrine levels	Skeletal muscle (quadriceps femoris muscle) of patients with septic shock	Strong association between production of muscle lactate and plasma epinephrine concentration and activation of Na^+K^+ ATPase

DO_2=critical oxygen delivery. PO_2=partial pressure of oxygen.

Table 2: **Evidence that hyperlactataemia in critical illness is not due to hypoxia**

concentrations of lactate in the blood, cerebral spinal fluid, and intracellularly.[75]

Finally, if inadequate perfusion was the cause of hyperlactataemia, methods to increase systemic or regional oxygen transport to supranormal values would correct hyperlactataemia. However, data suggest that patients with sepsis and increased lactate concentrations do not have an oxygen debt and do not respond to iatrogenic attempts to increase oxygen delivery.[76,77]

So-called lactate clearance has been promoted as a major goal of haemodynamic resuscitation in critically ill patients with sepsis. This concept has been proposed as an indicator of resolution of global tissue hypoxia.[78,79] However, such inferences fail on several grounds. First, the term lactate clearance is scientifically incorrect; clearance is the removal of a substrate from a unit of volume over a unit of time, typically expressed in millilitre per min. These investigators used the term lactate clearance to actually describe the rate of decrease in blood lactate concentration over time. Second, whether the rate of decrease was due to increased removal (metabolism), decreased production, dilution because of fluid resuscitation, or all the above in different combinations, is unknown.[80] Thus, the notion of so-called lactate clearance has no logical validity and is not associated with oxygen debt or tissue hypoxia.

If stress hyperlactataemia is not a consequence of insufficient oxygen, another explanation needs to be considered. In this regard, sepsis-associated inflammation and endogenous and exogenous catecholamines induce accelerated aerobic glycolysis.[81] Lactate production during shock states is linked to accelerated aerobic glycolysis through β_2-receptor stimulation,[70] and muscle lactate production during sepsis is associated with secretion of plasma epinephrine.[71] This state arises when the rate of carbohydrate metabolism exceeds the oxidative capacity of the mitochondria. Pyruvate is produced by an increased influx of glucose, but also by muscle protein catabolism, releasing amino acids subsequently transformed into pyruvate and thereafter lactate.[82] This increase in pyruvate concentration will ultimately drive lactate production by a mass effect. Findings of studies in human beings and animals have shown that epinephrine increases lactate formation by an increase in the Na^+K^+ ATPase activity.[70] This effect of epinephrine on muscle lactate formation is mediated by β_2 stimulation.[83,84] Levy and coworkers[51] confirmed this finding using selective β_2 blockade and muscle microdialysis during endotoxic shock. Epinephrine increases cyclic AMP production, thereby inducing stimulation of glycogenolysis and glycolysis with concomitant production of ATP and activation of the Na^+K^+ ATPase pump. This activation consumes ATP, leading to the generation of ADP. ADP, via phosphofructokinase stimulation, reactivates glycolysis and hence generates more pyruvate and, consequently, more lactate. Moreover, the role of Na^+K^+ ATPase pump stimulation was further confirmed by Levy and coworkers[68] who reported that muscle lactate production was totally inhibited by the sodium pump inhibitor, ouabain. Of clinical importance, in patients with shock, the ability to increase glycolysis and lactate production upon epinephrine stimulation is associated with improved prognosis,[72] suggesting that this response is adaptive. Additionally, lactate and pyruvate

concentrations measured by microdialysis are higher in muscle than in arteries, supporting the notion of lactate production in muscle (40% of total cell mass) during septic shock.[68] The lungs also seem to play an important part in lactate release in patients with septic shock,[67] probably associated with the presence of infiltrating inflammatory cells.[85]

The use of isotope dilution methods has enabled researchers to show that, in severe sepsis, the turnover of both glucose and lactate are increased. Glucose turnover might increase lactate production via glycolysis. Insulin resistance as seen in sepsis also favours glycolysis and glucose-lactate cycling.[4] Studies of labelled exogenous lactate in patients with sepsis show that oxidation is the major fate (50–60%) of infused lactate. By contrast, conversion of lactate into plasma glucose (Cori cycle) seems to be quantitatively limited. However, the amount of lactate not oxidised or converted into plasma glucose remains substantial (approximately 30%) and lactate becomes a substrate for glycogen synthesis by the liver and the kidney.

Cardiac surgery and cardiogenic shock and hyperlactataemia

Hyperlactataemia in patients who have undergone cardiac surgery is fairly common.[6] Irrespective of whether hyperlactataemia is early (admission) or late (post-admission), it is strongly associated with mortality.[86] Most studies refer to tissue hypoxia or organ oxygen debt as the main explanations for hyperlactataemia.[87] However, when measured by microdialysis during cardiopulmonary bypass, no association was found between tissue and plasma lactate concentrations.[88] Instead, other studies found hyperlactataemia and local lung production after cardiopulmonary bypass,[67,89] and no clinical or haemodynamic evidence of tissue hypoperfusion was found in a group of patients who had undergone cardiopulmonary bypass and developed hyperlactataemia.[90] In an animal study, even when experimental cardiogenic shock was induced and oxygen transport variables and mitochondria function were measured, no tissue hypoxia or expression of HIF-1α were found.[66]

Hyperglycaemia and administration of epinephrine, norepinephrine, and dobutamine are often associated with hyperlactataemia after cardiac surgery.[6,90] As has been reported in animal models of cardiogenic shock,[91] and also in patients with cardiogenic shock using isotope tracers,[92] glycolysis and gluconeogenesis are markedly increased and associated with hyperlactataemia. Stimulation of β-adrenergic receptors increases plasma glucose concentration, thereby increasing the substrates for glycolysis and lactate production.[93]

Using an infusion of labelled lactate in patients with cardiogenic shock and healthy volunteers, researchers estimated that 50% of this lactate was oxidised and 20% was used for glucose synthesis, without differences between the two groups.[4] Half-molar (0·5 M) sodium lactate solution was well tolerated for fluid resuscitation in patients after cardiac bypass surgery and was associated with an improved cardiac index.[94] Normal hepatic lactate-based gluconeogenesis has been recorded during cardiogenic shock.[92]

Liver failure and hyperlactataemia

Acute liver failure is strongly associated with hyperlactataemia, which has prognostic importance in this group of patients.[95,96] Liver dysfunction is believed to contribute to hyperlactataemia via decreased clearance.[97] However, when isotope tracers and lactate infusion were used in patients before and after major hepatectomy, lactate clearance, oxidation, and transformation into glucose were not different to healthy controls.[98] This finding suggests that decreased hepatic lactate utilisation is not the only mechanism in the pathogenesis of hyperlactataemia of liver failure. Moreover, hyperlactataemia during liver failure is associated with a net increased production of hepatic lactate secondary to increased metabolic rate and accelerated glycolysis.[5,96] The lungs also seem to have a role in lactate production during acute liver failure.[99] Finally, in patients with cirrhosis, hyperlactataemia is related to portal pressure, suggesting that accelerated glycolysis in the splanchnic region might play a part.[100]

Conclusions

Stress hyperlactataemia is ubiquitous in human beings during exercise and pathophysiological stress and is a strong predictor of mortality in critical illness. However, the hyperlactataemia is not a consequence of anaerobic glycolysis, tissue hypoperfusion, or cellular hypoxia. In all studied settings, lactate production happens under fully aerobic conditions. Such hyperlactataemia is probably indicative of a stress response, with increased metabolic rate and sympathetic nervous system activation inducing a state of accelerated glycolysis and modified bioenergetic supply. Lactate is not a waste product, but is instead a source of energy for the same cell in which it was produced (intracellular lactate production), for nearby cells (cell-to-cell lactate shuttle), or for the whole body (Cori cycle). Clinicians need to understand that stress hyperlactataemia should no longer be seen as a biomarker of hypoxia or anaerobic glycolysis, but as a major protective component of the stress response.

Conflicts of interest

We declare that we have no conflicts of interest.

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