Lactate physiology in health and disease

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Key points

Blood lactate concentrations reflect the balance between lactate production and clearance.

Glycolysis, gluconeogenesis and pyruvate conversion to and from lactate are linked with NAD^+ and NADH.

Failure of oxidative mechanisms can affect both production and clearance of lactate.

Lactate concentrations >5 mmol $litre^{-1}$ with severe metabolic acidosis predicts high mortality.

Impaired lactate clearance, rather than hypoxic tissue production of lactate, is the cause of hyperlactaemia in stable septic patients.

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The normal plasma lactate concentration is 0.3–1.3 mmol $litre^{-1}$. Considered once as a special investigation, it is increasingly measured automatically with the blood gas analysis. Plasma concentrations represent a balance between lactate production and lactate metabolism. In humans, lactate exists in the levorotatory isoform.

Normal lactate production

Glycolysis in the cytoplasm produces the intermediate metabolite pyruvate (Fig. 1). Under aerobic conditions, pyruvate is converted to acetyl CoA to enter the Kreb's cycle. Under anaerobic conditions, pyruvate is converted by lactate dehydrogenase (LDH) to lactic acid. In aqueous solutions, lactic acid dissociates almost completely to lactate and H^+ (pKa at 7.4 = 3.9) (Fig. 2). Consequently, the terms lactic acid and lactate are used somewhat interchangeably. Lactate is buffered in plasma by $NaHCO_3$.

Tissue sources of lactate production include erythrocytes, perivenous hepatocytes, skeletal myocytes and skin. Basal lactate production is 0.8 mmol kg^{-1} h^{-1} (1300 mmol day^{-1}).

Measurement of lactate

Spectrophotometric analysers measure lactate in deproteinized blood by using LDH to oxidize lactate in the presence of nicotinamide adenine dinucleotide (NAD^+) to pyruvate. Light at 340 nm is used to measure the dihydronicotinamide adenine dinucleotide (NADH) formed. This is related to the lactate concentration. Lactate measurements obtained from blood gas analysers use a modified amperometric cell. The cell contains the enzyme lactate oxidase, which produces hydrogen peroxide from lactate. The hydrogen peroxide is oxidized at a platinum anode producing a current proportional to the lactate concentration. The current from a second electrode which functions without the enzyme is subtracted from the measuring electrode to eliminate interference.

The amperometric cell reads 13% higher than the spectrophotometric analyser; correcting for haematocrit reduces this difference.[1] *In vitro* red cell glycolysis leads to false elevation of whole blood lactate. Specimens that are not immediately analysed should be stabilized. This can be achieved by cooling, protein precipitation or by addition of glycolytic inhibitors.

Lactate and lactic acidosis

Hydrogen ions released from the dissociation of lactic acid can be used in the production of ATP by oxidative phosphorylation. Impairment of oxidative pathways during lactate production results in a net gain of H^+ and acidosis occurs. (Oxidative phosphorylation during severe exercise prevents acidosis despite massive lactate production.)

NADH and NAD^+

Glycolysis requires NAD^+ (Fig. 1) produced, in part, by the conversion of pyruvate to lactate. The supply of NADH controls the rate of conversion of pyruvate to lactate. Tissues such as the heart, which are required to generate large amounts of ATP, require the conversion of pyruvate to acetyl CoA. In order to keep levels of NADH low, shuttles are used to help transport electrons across the mitochondrial membrane and oxidize NADH back to NAD^+. The malate–aspartate shuttle is the principle mechanism. The glycerol–phosphate shuttle plays a secondary role. They are known collectively as the ox-phos shuttle (Fig. 3). If the rate of glycolysis rises to a point where the ox-phos shuttle is overwhelmed, concentrations of NADH rise and lactate production regenerates NAD^+, raising lactate concentrations.

Normal lactate metabolism

The liver removes 70% of lactate. Uptake involves both a monocarboxylate transporter and the less efficient process of diffusion (important at concentration >2 mmol $litre^{-1}$).

Continuing Education in Anaesthesia, Critical Care & Pain | Volume 6 Number 3 2006 doi:10.1093/bjaceaccp/mkl018

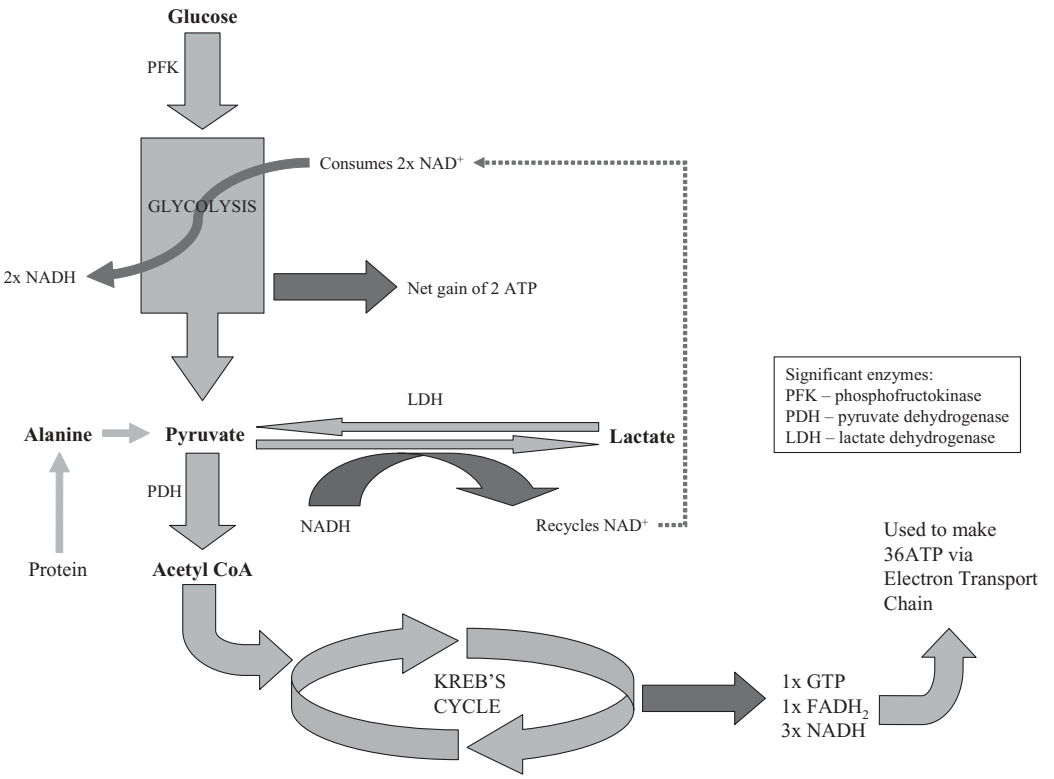

Fig. 1 Glycolysis, Kreb's cycle and oxidative phosphorylation.

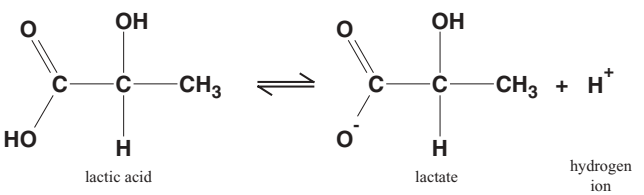

Fig. 2 The dissociation of lactic acid.

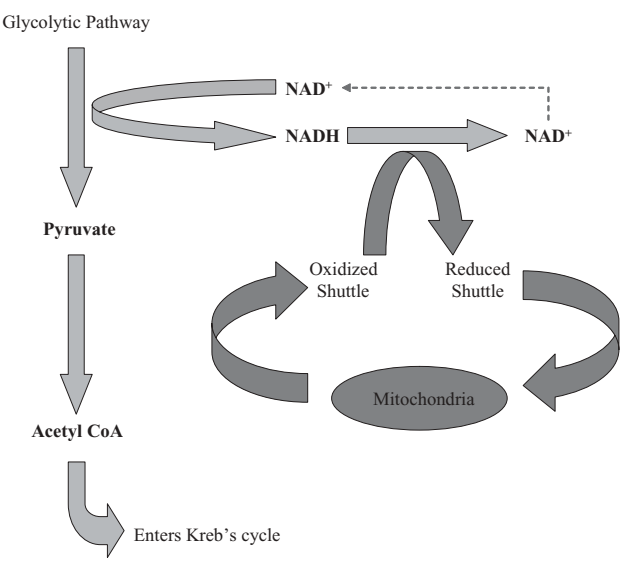

Fig. 3 The ox-phos shuttle.

Within the periportal hepatocytes, metabolism involves the processes of gluconeogenesis and, to a lesser extent, oxidation to CO_2 and water (Fig. 4). Mitochondria-rich tissues such as skeletal and cardiac myocytes and proximal tubule cells remove the rest of the lactate by converting it to pyruvate. This requires NAD^+ supplied by the ox-phos shuttle (Fig. 4). Less than 5% of lactate is renally excreted.

Causes of hyperlactaemia

Increased lactate production

Hyperlactaemia (>5 mmol litre^{-1}) is conventionally divided into Type A, in which tissue hypoxia results in faster production than removal, and Type B, in which overt tissue hypoxia does not play a role.[2] Type B has been further sub-divided depending on whether it is caused by underlying disease (B1), drugs and toxins (B2) or inborn errors of metabolism (B3).[3] This classification has the tendency to over-simplify a frequently multifactorial situation during critical illness. Furthermore, it is not useful functionally (Table 1).

Table 1 Causes of hyperlactaemia considered in terms of increased production and decreased clearance. *There is no evidence that hypoxia is the stimulus of lactate production during vigorous exercise

	Examples	Type
Increased production		
Increased rate of glycolysis		
Increased AMP—imbalance between ATP supply and demand	Hypoxaemia, anaemia, hypoperfusion, shock, CO poisoning	A
	Severe exercise	A
Catecholamines	Phaeochromocytoma	B1
	Salbutamol, epinephrine infusion	B2
Unregulated substrate entry into glycolysis	Fructose infusion	B2
Accumulation of pyruvate		
Pyruvate dehydrogenase inactivity	Thiamine deficiency	B3
	Congenital abnormality of pyruvate dehyrogenase	B3
	Inhibition by endotoxin	B2
Alanine formation	Critical illness	B2
	Malignancy	B2
Defects of oxidative processes	Pyruvate carboxylase deficiency	B3
	Cyanide toxicity	B2
Decreased clearance		
Hepatic metabolism		
Impaired oxidative metabolism	Impaired liver blood flow, enzyme defects, cyanide toxicity	A, B3, B1
Impaired gluconeogenesis	Biguanides, alcohol intoxication, diabetes	B1, B1, B2
Mitochondria-rich tissue metabolism	Hypoxaemia, anaemia, regional hypoperfusion, shock	A
	Enzyme defects, cyanide toxicity	B3, B1
Renal excretion	Renal excretion normally accounts for <5% of lactate clearance. This fraction may rise during hyperlactaemia	

Increased glycolysis. To support an increase in glycolysis, NAD^+ from the conversion of pyruvate to lactate, is required. The activity of phosphofructokinase (PFK) is rate limiting. The fall in ATP following, for example, hypoxaemia, anaemia, hypoperfusion, severe exercise and carbon monoxide poisoning all serve to stimulate PFK as AMP rises. Additionally, both endogenous secretion and exogenously administered catecholamines also stimulate glycolysis.

With severe exercise, type II myocytes produce large amounts of lactate (concentrations may rise to 25 mmol $litre^{-1}$ without any long-term sequelae; see above). This provides some of the increased cardiac energy requirements (Fig. 4). Following severe exercise and during a gentle 'warm-down', type I muscle fibres account for an increased proportion of lactate metabolism.

Unregulated glycolysis, induced by fructose containing parenteral feeding regimes, is now of historical interest.

Errors of metabolism. The activity of pyruvate dehydrogenase (Fig. 1) is impaired in inborn errors of metabolism, thiamine deficiency and by endotoxin.[4] Protein catabolism, resulting from critical illness or malignancy, produces alanine, which is converted to pyruvate. Any defects of Kreb's cycle or the electron transport chain will cause pyruvate to accumulate.

Decreased hepatic lactate clearance

The liver receives 25% of cardiac output. The hepatic portal vein supplies 75% of liver blood flow and 50–60% of its oxygen. Changes to hepatic blood flow and hepatic oxygen supply, as well as intrinsic hepatic disease, all affect the capacity of the liver to metabolize lactate.

Only when the liver blood flow is reduced to 25% of normal is there a reduction in lactate clearance. With severe shock, lactate uptake by the monocarboxylate transporter becomes saturated, the development of an intracellular acidosis inhibits gluconeogenesis and reduced liver blood flow delivers less lactate for metabolism. Under anaerobic conditions, glycolysis becomes the predominant mode of hepatic energy production. As such, the liver becomes a lactate-producing organ rather than using lactate for gluconeogenesis (Fig. 4).

Oral hypoglycaemic drugs. Gluconeogenesis supplies NAD^+ required to convert lactate to pyruvate (Fig. 4). Biguanide oral hypoglycaemic drugs inhibit hepatic and renal gluconeogenesis (although metformin only seems to affect lactate metabolism in the presence of impaired renal function). Metformin is contraindicated in renal and hepatic impairment. The supply of NAD^+ is vulnerable to demands from other enzyme systems, such as alcohol dehydrogenase. This becomes significant when activated by ethanol intoxication. Gluconeogenesis is impaired in type I diabetes.

Hartmann's solution. The strong ion difference in Hartmann's solution is 28 meq $litre^{-1}$, closer to the normal value of 40-42 meq $litre^{-1}$ than saline 0.9% where the SID is zero. Hartmann's solution, therefore results in less hyperchloraemic acidosis than saline 0.9%. The lactate (29 mmol $litre^{-1}$) will act as a strong ion and may transiently result in acidosis until it is metabolized by the liver.[5]

Sepsis

Although overproduction of lactate by phagocytic cells in response to endotoxin or tissue trauma accounts for some of

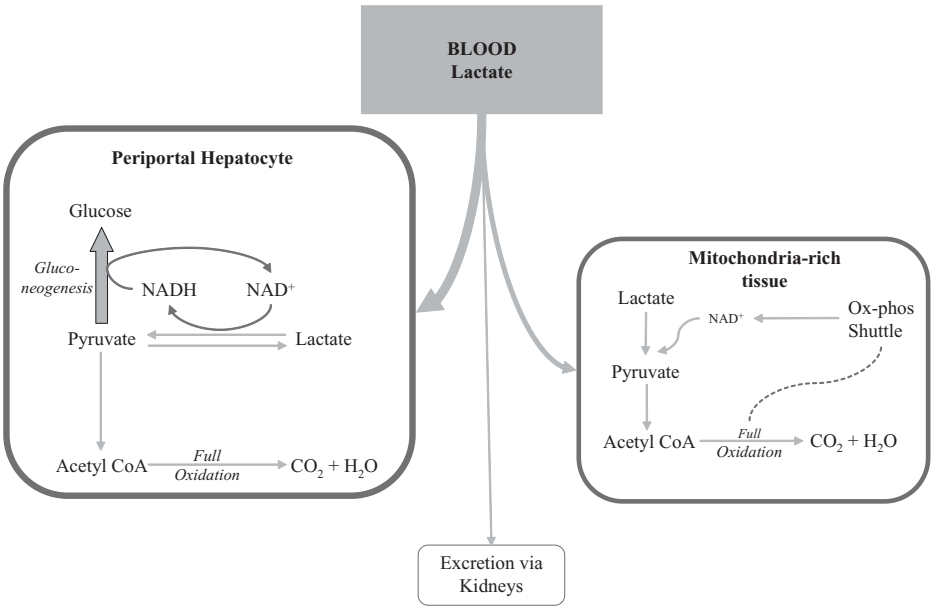

Fig. 4 Principle modes of lactate removal from plasma.

the rise in lactate in septic states, a decrease in hepatic lactate extraction and utilization also occurs.

Chronic disease

The reduced ability of the chronically diseased liver to handle lactate becomes evident when peripheral production is increased or further liver injury occurs.

Decreased extra hepatic metabolism

Mitochondria-rich tissues will fail to metabolize lactate when their oxygen supply fails or if there are intrinsic abnormalities of oxidative pathways. Under such circumstances, like the liver, they will become lactate-producing rather than consuming tissues.

Reduced renal excretion

The kidneys handle lactate by excretion, gluconeogenesis and oxidation. As the renal threshold is 6–10 mmol litre^{-1}, renal excretion is significant only with hyperlactaemia.

Lactate and critical illness

Blood lactate concentrations >5mmol litre^{-1} in patients with severe acidosis pH <7.35 or base deficit greater than 6 carries a mortality of 80%.[6]

Cardiac arrest and resuscitation

Whole body hypoxia occurring during cardiac arrest or severe hypovolaemia triggers anaerobic metabolism. Lactate concentrations directly reflect cellular hypoxia. Consequently, during in-hospital cardiac arrest and 1 h after return of spontaneous circulation, lactate concentrations are predictive of survival.[7]

Sepsis

During systemic inflammatory response syndrome (SIRS) or early sepsis, hyperlactaemia may reflect tissue hypoxia. Early enhancement of oxygen delivery improves outcome.[8] Interpreting lactate concentrations in patients with established sepsis is difficult. Stable septic patients have elevated oxygen delivery and tissue oxygen levels generally exceed those that trigger anaerobic metabolism. Impaired lactate clearance is usually more significant than increased production. Aerobic lactate production in such patients may be involved in modulation of carbohydrate metabolism under stress.[9] Dichloroacetate enhances the activity of pyruvate dehydrogenase and lowers blood lactate concentrations in septic patients but has no effect on haemodynamics or survival.[10]

Intestinal infarction

Gut hypoxia causes anaerobic metabolism. The liver receives more lactate from the portal vein. Initially, this is oxidized or converted to glucose by the periportal hepatocytes. Bacterial translocation and profound fluid shifts contribute to circulatory collapse. Global oxygen delivery falls. Endogenous catecholamine release attempts to support the circulation but will also increase glycolysis and lactate formation. As shock develops hepatic blood flow falls and intracellular acidosis inhibits gluconeogenesis from lactate. The liver produces rather than clears lactate. Intestinal bacteria metabolize glucose and carbohydrate

to D-lactate. This is only slowly metabolized by human LDH and contributes to the escalating lactic acidosis.

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Please see multiple choice questions 28–30.