CHEST

Lactic Acidosis in Sepsis: It's Not All Anaerobic

Implications for Diagnosis and Management

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Increased blood lactate concentration (hyperlactatemia) and lactic acidosis (hyperlactatemia and serum pH < 7.35) are common in patients with severe sepsis or septic shock and are associated with significant morbidity and mortality. In some patients, most of the lactate that is produced in shock states is due to inadequate oxygen delivery resulting in tissue hypoxia and causing anaerobic glycolysis. However, lactate formation during sepsis is not entirely related to tissue hypoxia or reversible by increasing oxygen delivery. In this review, we initially outline the metabolism of lactate and etiology of lactic acidosis; we then address the pathophysiology of lactic acidosis in sepsis. We discuss the clinical implications of serum lactate measurement in diagnosis, monitoring, and prognostication in acute and intensive care settings. Finally, we explore treatment of lactic acidosis and its impact on clinical outcome.

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> "I have yet to see any problem, however complicated, which, when you looked at it in the right way, did not become still more complicated."
>
> –Poul William Anderson

Blood lactate concentration is often measured in patients with severe sepsis and particularly those in septic shock. Lactic acidosis has been traditionally interpreted as a biological marker of tissue hypoxia because of inadequate oxygen delivery and as a predictor of adverse outcome.[1] This view is too simplified and does not take into consideration the many causes on increased lactate accumulation that can occur in the absence of tissue hypoxia or in addition to tissue hypoxia. Lactate is not just metabolic waste arising from anaerobic glycolysis. Rather, it is an important energy "shuttle" whose production is triggered by a variety of metabolites even before the onset of anaerobic metabolism as part of an adaptive response to a hypermetabolic state and, in particular, during sepsis.[2] Here, we review hyperlactatemia and lactic acidosis in sepsis and implications for diagnosis and treatment.

Lactic acid has been recognized as a metabolite associated with sepsis for almost 200 years[3] and with tissue hypoxia for more than 100 years.[4] In 1961, Huckabee first

ABBREVIATIONS: ATP = adenosine triphosphate; NADH = nicotinamide adenine dinucleotide hydride; NAD^+ = oxidized form of nicotinamide adenine dinucleotide; Na^+-K^+-ATPase = sodium-potassium-adenosine triphosphatase; RCT = randomized control trial

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recognized that blood lactate concentration could be increased out of proportion to pyruvate and associated with acidosis (lactic acidosis) or, in contrast, that blood lactate concentration could be increased, accompanied by a proportional increase in pyruvate without acidosis.[5,6] In 1976, Cohen and Woods divided hyperlactatemia into two categories: lactic acidosis associated with clinical evidence of inadequate tissue oxygenation (type A) and hyperlactatemia in which clinical evidence of tissue hypoxia was absent (type B). Type B hyperlactatemia was further subdivided into B_1, in which hyperlactatemia was associated with certain underlying diseases such as liver failure; B_2, in which hyperlactatemia was due to drugs or toxins; and B_3, in which hyperlactatemia was caused by inborn errors of metabolism.[7]

Lactate Production

Under normal conditions, lactate is produced at the remarkably high rate of approximately 1.5 mol per day; thus, lactate is not simply a waste product indicating anaerobic metabolism. Rather, the "lactate shuttle" theory highlights the role of lactate in the distribution of oxidative and gluconeogenic substrates as well as in cell signalling.[8,9] Lactate produced in one location can be used as a preprocessed fuel for mitochondrial respiration by numerous distant tissues or can be used by the liver in gluconeogenesis.[10,11] Normal lactate production arises mainly from skeletal muscle; skin, brain, intestine, and erythrocytes also contribute.[12] The lungs can create lactate during acute lung injury without tissue hypoxia,[13,14] and leukocytes also generate lactate during phagocytosis or when activated in sepsis.[15] In pathological conditions in which oxygen delivery is limited, lactate generation develops in other tissues.

Lactate arises from the metabolism of glucose (Fig 1). Glycolysis metabolizes glucose to pyruvate, which is catalyzed by phosphofructokinase in the Embden-Meyerhof pathway.[16] Further metabolism of pyruvate follows one of two routes. First, under aerobic conditions, pyruvate enters mitochondria and is converted to acetyl coenzyme A by pyruvate dehydrogenase, which enters the tricarboxylic acid (Krebs) cycle. Note that thiamine diphosphate is a coenzyme required for the catalytic activity of several enzymes involved in two-carbon transfers, including pyruvate dehydrogenase. Once within the Krebs cycle, stepwise metabolism of acetyl coenzyme A occurs in concert with stepwise transport of electrons in high-energy states down to lower energy states with the production of adenosine triphosphate

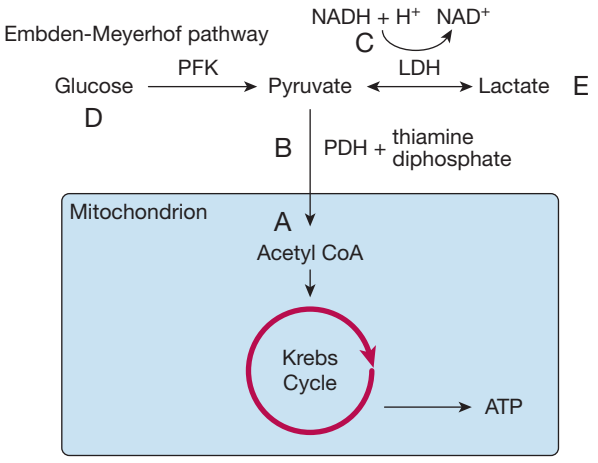

Figure 1 – *The pathway from glycolysis to pyruvate to lactate production is illustrated, with key features leading to increased lactate concentrations labeled in red. A, Lactic acidosis from tissue hypoxia. Anaerobic metabolism reduces flux through the Krebs cycle so pyruvate is shunted toward lactate. B, Hyperlactatemia not directly resulting from tissue hypoxia. Thiamine deficiency reduces flux of pyruvate to the Krebs cycle, increasing lactate production. C, A reducing environment has increased NADH/NAD+, which favors lactate production. D, Increased glycolytic flux through the Embden-Meyerhof pathway results in increased pyruvate availability, potentially beyond the capacity of mitochondrial respiration to metabolize pyruvate, so lactate production increases. E, Decreased lactate clearance also increases lactate concentrations even in the absence of tissue hypoxia. ATP = adenosine triphosphate; CoA = coenzyme A; LDH = lactate dehydrogenase; NADH = nicotinamide adenine dinucleotide hydride; NAD+ = nicotinamide adenine dinucleotide; PDH = pyruvate dehydrogenase; PFK = phosphofructokinase.*

(ATP) molecules. Oxygen provides a very low-energy electron sink at the end of the electron transport chain, allowing generation of 38 ATP molecules for each molecule of metabolized glucose.

The second route for pyruvate is conversion to or from lactate in the cytosol. This reaction is bidirectionally catalyzed by lactate dehydrogenase, resulting in a normal lactate:pyruvate ratio of approximately 10:1. When sufficient oxygen is not available, the Krebs cycle cannot metabolize pyruvate so lactate is generated (Fig 1A). This is tissue hypoxia. However, lactate production independent of tissue hypoxia can also occur. Entry of pyruvate into the Krebs cycle, catalyzed by pyruvate dehydrogenase, can be limited by thiamine deficiency, which results in diversion of pyruvate toward lactate production (Fig 1B). The conversion of pyruvate to lactate requires nicotinamide adenine dinucleotide hydride (NADH) and H^+. Conditions which result in a reducing cellular environment (elevated NADH/oxidized form of nicotinamide adenine dinucleotide [NAD^+]), such as ethanol ingestion and ketoacidosis, promote production of lactate independent of tissue oxygenation (Fig 1C). Importantly, in patients with sepsis, increased glycolytic flux results in increased

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