

A perspective on Serum Lactic acid, Lactic Acidosis in a Critical Care Unit

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Abstract

Breast cancer is one of the major surgical problems encountered in Libya. Lactic acidosis is a universal complication in breast cancer patients and can be considered a possible prognostic marker. Therefore, it will be beneficial to correctly understand and review the biochemistry underlying lactic acidosis and its possible significance as a prognostic marker in critical care patients, including breast cancer.

Keywords: lactic acidosis, critical care patients.

Introduction

Breast cancer is one of the major surgical problems encountered in Libya [1]. Lactic acidosis is a complication in breast cancer patients and can be considered a possible prognostic marker. Therefore, it will be beneficial to correctly understand and review the biochemistry underlying lactic acidosis and its possible significance as a prognostic marker in critical care patients, including breast cancer.

Lactic acidosis is one of the common metabolic acidotic conditions encountered in the Critical Care Unit. It occurs frequently in patients with shock and myocardial contractility. Patients with lactic acidosis reportedly have high mortality.

Lactic acidosis is a pathological state diagnosed when the serum concentration of lactate or lactic acid remains persistently at $>5\text{mmol/L}$ or greater and significant acidemia is noted with blood $\text{pH} < 7.35$ (normal concentration of blood lactate is $1\text{-}2.0\text{mmol/L}$) [2].

According to the Cohen-Woods classification [3] the causes of lactic acidosis are distinguishable as two types - Type A and Type B.

TYPE A: It occurs in hypoperfusion and hypoxia.

• **Tissue hypoxia** is seen in carbon monoxide poisoning, severe asthma and severe anemia.

• **Hypoperfusion** occurs in state of shock (cardiogenic, hemorrhagic, septic, regional ischemia)

TYPE B: It occurs when there is no clinical evidence of hypoperfusion. It is subdivided into 3 subtypes:

(i)B1 is associated with acquired diseases like diabetes mellitus, grand mal seizures, hepatic failure, septicemia, malignancies, pheochromocytoma, post cardiopulmonary bypass, renal failure, thiamine deficiency, thyroid storm etc.

(ii)B2 is associated with metabolites, drugs and toxins like acetaminophen, biguanides, cocaine, diethyl ether, epinephrine, norepinephrine, ethanol, ethylene glycol, isoniazid, lactulose, methanol, nalidixic acid, niacin, nitroprusside, antiretroviral therapy, paraldehyde, parenteral nutrition, terbutaline, theophylline etc.

(iii)B3 is due to inborn errors of metabolism (congenital lactic acidosis) e.g. Glucose-6 phosphate dehydrogenase deficiency, fructose-1-6 diphosphatase deficiency, pyruvate carboxylase deficiency, organic aciduria, Leigh's disease, Alpers disease and mitochondrial encephalopathies etc.

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Lactate Metabolism

Lactic acid is the end product of anaerobic glycolysis. It is responsible for the generation of two ATP molecules of which provide energy during anaerobic conditions. This reaction is catalyzed by the enzyme lactate dehydrogenase (LDH), requiring nicotinamide adenine dinucleotide (NAD) as the coenzyme. It is by this reaction that the oxidized form of NAD is generated, essential for one of the glycolytic enzymes, glyceraldehyde phosphate dehydrogenase, to continue the glycolysis process.



This reaction occurs within the cytosol (a cytosolic process) in the final step of glycolysis [4]. In the basal physiologic state, the reaction favors the formation lactate from pyruvate, in a 10:1 ratio, approximately [5]. This reduction of the pyruvate is the only known pathway for lactate production, offering a unique way of monitoring the anaerobic metabolic processes (Fig. 1).

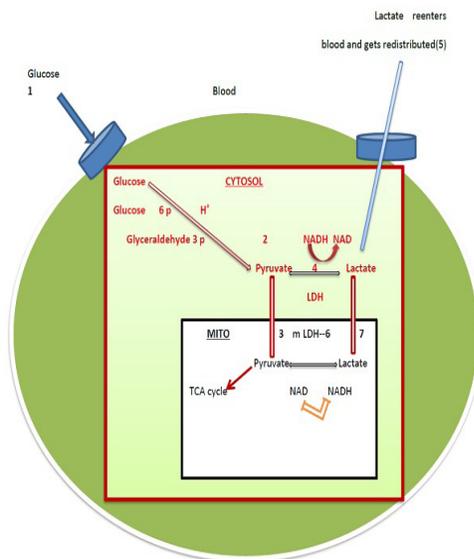


Figure 1.

The processes involved in the lactate shuttle hypothesis

The lactate pathway assumes that (1) glucose enters the cell, where it is sequentially broken down to pyruvate; (2) pyruvate enters the mitochondrion, continuing the respiration process in the tricarboxylic acid (TCA) cycle; (3) lactate is subsequently formed via the lactate dehydrogenase (LDH) reaction (4) and is then exported from the cytosolic compartment via the monocarboxylate transporter (MCT) mechanism (5), from where it is redistributed to several functional sites. Note the suggested presence of mitochondrial lactate dehydrogenase (mLDH) (6), which forms the scaffolding of the intracellular shuttle system (7).

Blood lactate levels which are a reflection of the balance between the production and clearance of lactate, have garnered significant scientific interest over the past few decades. The normal blood lactate level is lesser than 2 mmol/L [4]. However, under normal physiologic conditions, approximately 1500 mmol of lactate is produced daily, primarily from the skeletal muscle, skin, brain, intestine, and red blood cells [4-5]. Lactate clearance occurs principally in the liver (60%), with vital support from the kidneys (30%) and to a lesser extent from other organs (heart and skeletal muscle) [6]. Utilization occurs via the Cori cycle where the lactate is converted back to pyruvate and eventually to glucose through gluconeogenesis [7]. It has been shown

that patients with chronic liver disease (usually grade III or IV encephalopathy) [8] reveal a reduced rate of lactate clearance, which thus contributes to the elevated levels in the blood [9]. Besides the metabolic clearance mechanisms, lactate can also be excreted by the kidneys once the renal threshold is crossed (approximately 5 mmol/L) [4-5]. Thus, any form of hepatic or renal impairment can alter the lactate clearance.

Lactic acidosis is typically present in states of shock when tissue oxygen delivery (DO₂) is insufficient to meet the cellular demand. In this classic type A lactic acidosis, increased flux occurs through the glycolytic pathway, leading to pyruvate accumulation.

During states of low oxygen tension, the pyruvate does not enter the mitochondria for oxidative phosphorylation. Hypoxia is known to inhibit the pyruvate dehydrogenase (PDH) complex [10] involved in the aerobic breakdown of pyruvate to acetyl coenzyme A (CoA) for entry into the Krebs cycle. It also is known to inhibit pyruvate carboxylase, which converts the pyruvate into oxaloacetate, early in the gluconeogenesis process. This results in the rapid accumulation of pyruvate, and subsequently the pyruvate metabolism shifts almost wholly toward lactate formation. Consequently, the intracellular lactate concentration rapidly rises, to ultimately be excreted into the bloodstream. Clinically significant lactate formation from low perfusion was most conspicuously observed in a group of patients in cardiogenic shock, by Levy et al. [11], where the lactate-pyruvate ratios were calculated at 40:1 as compared with the controls (10:1). Further evidence for the increased lactate production during states of shock came from Revelly et al. [12], who compared seven patients in cardiogenic shock and seven patients in septic shock against seven healthy controls. By continually infusing ¹³C-radiolabeled lactate and ²H-labeled glucose, they revealed that hyperlactatemia resulted from the overproduction of lactate and that the clearance process was similar in all three groups.

Excess lactate production could be one of the likely contributors to hyperlactatemia in critically ill patients. Levraut et al. [7] showed that in patients with hemodynamically stable sepsis, the elevated lactate levels are more related to the alterations in clearance than to overproduction of the lactate. The overall lactate metabolism of in critical illness is, therefore, a highly complex process with many factors influencing the blood lactate levels. Lactate on its own is probably not harmful and is shuttled to the tissues during states of stress as a carbon backbone energy fuel. Therefore, the elevated blood lactate levels may be more of an indicator of an underlying stress state and not necessarily the direct cause of the pathogenesis.

It has been shown that lactic acidosis could be a rare metabolic complication of cancer. The accumulation of lactic acid resulting in lactic acidosis in breast cancer patients has been presumed to be due to the occurrence of metastatic lesions [13]. Spechler et al. [14] showed that acidosis could be the cause of death in patients with small cell (oat cell) carcinoma of the lung. It has been shown that hypocapnia and metabolic alkalosis are also observed in such patients, prior to the onset of lactic acidosis, which are known to utilize the liver as an organ of lactate output, independent of the changes in the carbon dioxide tension [15].

Therefore, a careful estimation of the serum lactate and its metabolism may be one of the important components in a Critical Care Unit that warrants reconsideration in light of the recent studies, with focus on the Warburg effect and lactic acidosis [16].

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