Lactic Acidosis and Hyperlactatemia

B. Levy

Introduction

Traditionally, hyperlactatemia in critically ill patients and particularly those in shock was interpreted as a marker of secondary anaerobic metabolism due to inadequate oxygen supply inducing cellular distress [1]. Many arguments have since refuted this view [2]. With lactate metabolism being extensively described in classical biochemistry manuals, this chapter will focus only on those aspects as they relate to critically ill patients. Distinction between lactic acidosis, metabolic acidosis with hyperlactatemia, and isolated hyperlactatemia will also be addressed.

Lactate Metabolism [3]

Arterial lactate concentration is dependent on the balance between its production and consumption. In general, it is less than 2 mmol/l, although daily production of lactate is actually 1500 mmol/l. In physiological conditions, lactate is produced by muscles (25%), skin (25%), brain (20%), intestine (10%) and red blood cells (20%) which are devoid of mitochondria. Lactate is essentially metabolized by liver and kidney.

Lactate is produced in the cytoplasm according to the following reaction (Fig. 1):

\[
\text{Pyruvate} + \text{NAD} + \text{H}^+ \leftrightarrow \text{lactate} + \text{NAD}^+
\]

This reaction favors lactate formation yielding a 10-fold lactate/pyruvate ratio. Lactate therefore increases when production of pyruvate exceeds its utilization by the mitochondria. Pyruvate is essentially produced via glycolysis; hence any increase in glycolysis, regardless of its origin, can increase lactatemia. Pyruvate is essentially metabolized by the mitochondrial aerobic oxidation pathway via the Krebs cycle.

\[
\text{Pyruvate} + \text{coenzyme A} + \text{NAD} \Rightarrow \text{acetyl CoA} + \text{NADH} + \text{H}^+ + \text{CO}_2
\]

This reaction leads to the production of large quantities of ATP (36).

Generated lactate can be transformed into oxaloacetate or alanine via the pyruvate pathway or can be utilized directly by periportal hepatocytes (60%) to produce glycogen and glucose (neoglycogenesis and neoglucogenesis) (Cori cycle). The kidney also participates in the metabolism (30%) of lactate with the cortex classically
acting as the ‘metabolizer’ by neoglucogenesis and the medulla as a producer of lactate. The threshold of renal excretion is 5–6 mmol/l meaning that, physiologically-speaking, lactate is not excreted in urine.

Hence, lactatemia reflects a balance between production and utilization of lactate. Consequently, for the same etiological mechanism producing an increase in lactate, one can either observe a hyperlactatemia (if its metabolism decreases) or a normolactatemia. Understanding this concept is vital, notably to avoid treating solely a numerical value of lactate.

## Formation of Lactate in Cases of Tissue Hypoxia

By definition, hypoxia blocks mitochondrial oxidative phosphorylation [4], thereby inhibiting ATP synthesis and reoxidation of NADH. This leads to a decrease in ATP/ADP ratio and an increase of NADH/NAD ratio. A decrease in the ATP/ADP ratio induces both an accumulation of pyruvate which cannot be utilized by way of

![Fig. 1. Overview of carbohydrate metabolism](image-url)