BLOOD LACTATE CONCENTRATIONS IN SEPSIS

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Numerous studies have demonstrated that blood lactate levels increase in humans with sepsis and in animal models of sepsis [1-22]. Some of the mechanisms leading to this hyperlactatemia are well understood, but there may be others that have not been fully elucidated. Regardless of the mechanisms, a strong association between outcome and the degree of lactate elevation has been documented repeatedly in patients with sepsis [2-4,7,8,10,16,17,19,23,24]. Lactate thus serves as a marker for severity of illness in these patients and identifies those who are at high risk for clinical decompensation. Lactate levels correlate better with survival than either cardiac index or oxygen transport indices, and predict the development of multiple organ system failure (MOF) [2,3,16].

NORMAL, RESTING LACTATE METABOLISM

A cell’s ability to perform its requisite functions and maintain its own homeostasis requires a ready supply of chemical energy in the form of adenosine triphosphate (ATP). At rest, nearly all tissues of the body rely on aerobic metabolic pathways to produce ATP, derived predominately from glucose that is oxidized to carbon dioxide (CO₂) and water in a series of chemical reactions that can be summarized as [25]:

\[
\text{Glucose} + 6 \text{O}_2 \rightarrow 6 \text{CO}_2 + 36-38 \text{ATP}
\]
This overall process can be broken down into a simplified four step sequence that involves the reduced and oxidized forms of the enzyme cofactors nicotinamide adenine dinucleotide (NADH and NAD$^+$, respectively) and flavin dinucleotide (FADH$_2$ and FAD, respectively). The first 3 of these steps are summarized as:

\[
\text{Glucose} \rightarrow 2 \text{Pyruvate} \quad \text{PD} \rightarrow 2 \text{Acetate} \rightarrow 4 \text{CO}_2
\]

\[
2 \text{ATP} + 2 \text{NADH} \quad 2 \text{CO}_2 + 2 \text{NADH} \quad 2 \text{GTP} + 6 \text{NADH} + 2 \text{FADH}_2
\]

Conversion of one 6-carbon molecule of glucose to two 3-carbon molecules of pyruvate is actually a series of individual reactions, each enzymatically catalyzed in the cytosol [25]. Two molecules of ATP are produced directly in this first step. In the next step, the pyruvate molecules are transported into the mitochondria where they are decarboxylated to acetate by the pyruvate dehydrogenase (PDH) enzyme complex. Acetate then enters the Krebs’ cycle and is converted to carbon dioxide.

The fourth step, which also takes place in the mitochondria, utilizes NADH and FADH$_2$ to produce ATP by passing electrons from the cofactor molecules to oxygen, reducing the latter to water:

Tightly coupled to this electron transport process are oxidative phosphorylation reactions, depicted by the vertical arrows above, that generate ATP from adenosine diphosphate (ADP). Each intramitochondrial NADH molecule is thus convertible to 3 ATP molecules, whereas each FADH$_2$ molecule produces only 2 molecules of ATP.

For the 2 NADH molecules produced in the first step to be converted to ATP, they must first be translocated into the mitochondria. In brain and skeletal muscle cells this is accomplished by a shuttle reaction that takes place at the mitochondrial membrane and, in effect, converts the NADH into FADH$_2$ yielding 2 molecules of ATP per cytoplasmic NADH [25]. A more