# Update: Clinical Use of Plasma Lactate

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**KEYWORDS**

• Lactate • Hyperlactatemia • Shock • Sepsis • Dog • Cat

**KEY POINTS**

- Lactate is an important adaptive intermediary metabolite and serves as an alternative energy fuel. Lactate production ensures a rapid and continued cellular energy supply.
- Lactate production consumes hydrogen ions (originating from ATP hydrolysis), thereby mitigating acidosis.
- Pathologic hyperlactatemia usually correlates with disease severity and mortality in populations of animals but not necessarily in individuals.
- Lactate is a good prognostic indicator in conditions with high mortality. A normal lactate concentration is a better predictor of survival than a high lactate concentration is of death.
- Serial lactate measurement likely yields better prognostic information than a single measurement.

## INTRODUCTION

Traditionally described as a dead-end waste product of anaerobiosis, the lactate paradigm has shifted over the past few decades. Lactate is an essential, versatile metabolic fuel in cellular bioenergetics. In human emergency and critical care, lactate is used as a biomarker and therapeutic endpoint and evidence is growing in veterinary medicine supporting its clinical utility. Lactate production is a protective response providing ongoing cellular energy during tissue hypoperfusion or hypoxia and mitigating acidosis. Hence, hyperlactatemia is closely associated with disease severity but it is an epiphenomenon as the body attempts to protect itself. This article reviews lactate biochemistry, kinetics, pathophysiology, some practical aspects of measuring lactate, as well as its use in diagnosis, prognosis, and monitoring.

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## BIOCHEMISTRY

Lactic acid and lactate are not synonyms. Lactic acid, formula $CH_3CH(OH)COOH$, is a strong acid with a pKa of 3.8. At physiologic pH, lactic acid almost completely dissociates into lactate anions, $C_3CH(OH)COO^-$, and protons ($H^+$).[1] Lactate exists as 2 stereoisomers: L-lactate and D-lactate, the former being the predominant physiologic enantiomer, accounting for 95% to 99% of total body lactate in health.[2] Increased blood lactate concentration is termed hyperlactatemia. Hyperlactatemia may or may not be associated with acidemia depending on the cause of increased lactate concentration, concurrent acid/base disorders, and buffer reserves.

High-energy adenosine triphosphate (ATP), required for cellular metabolism, is generated via glycolysis, the tricarboxylic acid (TCA) cycle, the electron transport chain (ETC), and oxidative phosphorylation. Glycolysis occurs in the cytosol with or without oxygen, converting 1 mol of glucose to 2 mol of pyruvate with the concomitant production of 2 ATP and 2 reduced nicotinamide adenine dinucleotide (NADH). The TCA cycle, ETC, and oxidative phosphorylation are mitochondrial and obligatory aerobic processes. When the ATP molecules generated by glycolysis are used, protons are released into the cytosol. These $H^+$ enter the mitochondrion and are used to create the proton gradient required for the ETC and oxidative phosphorylation. Pyruvate enters the mitochondrion, undergoes decarboxylation producing acetyl coenzyme A, which then proceeds through the TCA cycle, the ETC, and oxidative phosphorylation, generating 36 mol of ATP.[3]

Under healthy, resting conditions, a small quantity of pyruvate is converted to lactate, catalyzed by the ubiquitous lactate dehydrogenase (LDH). NADH is oxidized to $NAD^+$ during this reversible cytosolic reaction and $H^+$ is consumed.[3]

$$\text{Pyruvate} + \text{NADH} + H^+ \leftrightarrow \text{lactate} + NAD^+$$

When there is a lack of cellular oxygen, pyruvate and $H^+$ cannot enter the mitochondria, and the TCA cycle and oxidative phosphorylation pathways slow down and $NAD^+$ stores are depleted. Pyruvate, $H^+$, and NADH rapidly accumulate in the cytosol, diverting pyruvate metabolism toward lactate formation through the upregulation of LDH activity.[4] Lactate formation is a protective mechanism, consuming pyruvate and $H^+$ and thereby mitigating acidosis.[5] In addition, pyruvate to lactate conversion oxidizes NADH and replenishes $NAD^+$ stores, fueling and accelerating glycolysis, which temporarily satisfies energy demands.[6] Once oxygen supply is restored, lactate is converted back to either pyruvate or glucose via gluconeogenesis.

Moderate to severe hyperlactatemia with concurrent metabolic acidosis is often described as lactic acidosis but glycolysis forms lactate ions rather than lactic acid. It is the accumulation of cytosolic $H^+$, originating from ATP hydrolysis, that causes acidosis rather than hyperlactatemia per se. Nevertheless, in acute anaerobic states, the quantitative approach to acid/base describes an associated equimolar production of $H^+$ ions for every 1 mmol/L of lactate with a concurrent decrease in standardized base excess of 1 mmol/L.[7]

Once formed, lactate can either be used within the same cell or transported out of the cell via proton-linked and sodium-coupled monocarboxylate transporters (MCTs).[8] Of the 14 MCTs identified so far, MCT1 and MCT4 are considered the 2 primary MCTs in mammalian skeletal muscle.[9] MCTs also play a crucial role in so-called lactate shuttles, transferring lactate between cell compartments, cells, tissues, and organs.[10] These lactate shuttles are present in striated muscle, in the brain, kidneys,