Lactic Acid: Brief History
5: LACTIC ACID: BRIEF HISTORY

Robergs et al identified that the discovery of lactic acid was in 1789 by Carl Wilhelm Sheele, a Swedish chemist. Sheele isolated an acid in sour milk samples. This origin of acid in milk led to the naming ‘lactic’, which means relating to milk. Continuing with their historical account, Robergs et al noted that by 1810 chemists had verified the presence of lactic acid in other organic tissues such as in meat and in blood. In 1833, the actual chemical formula for lactic acid was determined. Molecular formula of lactic acid is C$_3$H$_6$O$_3$.$^{(94)}$

By 1869, scientists observed different isomers (atomic compounds with different energy states) of lactic acid along with its formation in fermentation reactions. Fermentation is an enzyme-driven chemical change in an organic (has carbon) compound whereby the substance is split into simpler compounds. Since lactic acid is a naturally occurring molecule, originally detected in food products (and with a mild acidic taste), it has and continues to be used to acidify some foods and beverages as well as function as a food preservative.$^{(94)}$

The prevailing understanding regarding lactic acidosis in humans can be attributed to some early researchers of skeletal muscle biochemistry during exercise. Two noted original researchers were Otto Meyerhoff and Archibald V. Hill, who in 1922 both received a Nobel Prize for their research in the energy capabilities of carbohydrate metabolism in skeletal muscle. Robergs and colleagues (2004) point out that it was Meyerhoff who suggested that lactic acid was a side reaction to glycolysis (splitting of sugar) in the absence of oxygen. They continue that the research of Hill and Meyerhoff solidified the acceptance of lactic acid production and acidosis into the mind-set of academics in physiology and biochemistry, although this was primarily based from their (incomplete) observations of cell metabolism at that time. Robergs states, “...it is easy to comprehend how the Nobel prize
quality of work of Hill and Meyerhoff was proof enough to the scientific world at that time for the interpretation that lactate production and acidosis were cause-and-effect."

It is important to stress that this revealing and interesting history of acidosis and lactate exposes one important message. There really never was experimental research demonstrating a cause-effect relationship between lactate production and acidosis. Yet, the work of these early pioneers has been considered the absolute explanation of acidosis for more than 80 years (94).

5.1: LACTATE: NORMAL VALUE AND UNIT

The units of measurement of lactate vary between laboratories. Some use milligrams per deciliter (mg.dl\(^{-1}\)), whereas others use milimole per liter (mmol.l\(^{-1}\)) conversion between these units is based on knowing that the molecular weight of lactic acid is 90, hence

\[
\text{Mg.dl/L} = \text{mmol.l}^{-1} \times 9
\]

Or

\[
\text{Mmol/L} = \text{mg.dl}^{-1} \times 0.111
\]

The normal reference value for blood lactate at rest is 5-20 mg.dl\(^{-1}\)

Or it can be expressed in 0.5 to 2.2 mmol/L (95).

5.2: LACTATE PRODUCTION

It is necessary to understand the normal metabolic pathway of the energy system in human body before we understand that how lactate is produced and normal metabolic pathway is very well shown here in diagram of citric acid cycle.

The citric acid cycle — also known as the Tricarboxylic acid cycle (TCA cycle), or the Krebs cycle, is a series of chemical reactions used by all aerobic organisms to generate energy through the oxidation
of acetate derived from carbohydrates, fats and proteins into carbon
dioxide and chemical energy in the form of adenosine triphosphate
(ATP). In addition, the cycle provides precursors of certain amino acids
as well as the reducing agent NADH that is used in numerous other
biochemical reactions. Its central importance to many biochemical
pathways suggests that it was one of the earliest established components
of cellular metabolism and may have originated abiogenically\(^{(96)}\).

The name of this metabolic pathway is derived from citric acid (a
type of Tricarboxylic acid) that is consumed and then regenerated by
this sequence of reactions to complete the cycle. In addition, the cycle
consumes acetate (in the form of acetyl-CoA) and water, reduces NAD+
to NADH, and produces carbon dioxide as a waste byproduct. The
NADH generated by the TCA cycle is fed into the oxidative
Phosphorylation (electron transport) pathway. The net result of these
two closely linked pathways is the oxidation of nutrients to produce
usable chemical energy in the form of ATP\(^{(96)}\).
5.3: THE CITRIC ACID CYCLE

**Figure 30: Citric Acid cycle**
Lactate production occurs whenever the rate of pyruvate production from glycolysis exceeds glucose oxidation by the mitochondria. Therefore, for increased lactate production to be important physiologically, mitochondrial glucose oxidation must decrease under conditions known to result in increased gluconeogenesis.

All this process is shown in the figure given below\(^{(97)}\).
During rest and moderate exercise, some lactate continually forms in two ways. 1-energy metabolism of red blood cells that contain no mitochondria and 2-limitations posed by enzyme activity in muscle fibers with high glycolytic capacity. Any lactate that forms in this manner readily oxidized for energy in neighboring muscle fibers with high oxidative capacity or in more distant tissue such as the heart and ventilatory muscles. Consequently lactate does not accumulate because its removal rate equals its rate of production.\(^{(17)}\)
During intense exercise, the respiratory chain cannot keep up with the amount of hydrogen atoms that join to form NADH. NAD\(^+\) is required to oxidize 3-phosphoglyceraldehyde in order to maintain the production of anaerobic energy during glycolysis. During anaerobic glycolysis, NAD\(^+\) is “freed up” when NADH combines with pyruvate to form lactate. If this did not occur, glycolysis would come to a stop. However, lactate is continually formed even at rest and during moderate exercise. This occurs due to metabolism in red blood cells that lack mitochondria, and limitations resulting from the enzyme activity that occurs in muscle fibers having a high glycolytic capacity.

During power exercises such as sprinting, running, cycling when the rate of demand for energy is high, glucose is broken down and oxidized to pyruvate, and lactate is produced from the pyruvate faster than the tissues can remove it, so lactate concentration begins to rise. Once the production of lactate is occurs it regenerates NAD\(^+\), which is used up in the creation of pyruvate from glucose, and this ensures that energy production is maintained and exercise can continue. The increased lactate produced can be removed in following ways:

- Oxidation back to pyruvate by well-oxygenated muscle cells.
- Pyruvate is then directly used to fuel the citric acid cycle.
- Conversion to glucose via gluconeogenesis in the liver and release back into circulation; Cori cycle.
- If not released, the glucose can be used to build up the liver's glycogen stores if they are empty\(^{17}\).

A valuable waste product lactate should not be viewed as a metabolic waste product. To the contrary, it provides a valuable source of chemical energy that accumulates with intense exercise. When sufficient oxygen becomes available during recovery, or when exercise pace slows, NAD\(^+\) scavenges hydrogen’s attached to lactate to form ATP via oxidation. The carbon skeletons of the pyruvate molecules re-
formed from lactate during exercise become either oxidized for energy or synthesized to glucose in muscle itself or in the Cori cycle. The Cori cycle removes lactate and also uses it to replenish glycogen reserves depleted from intense exercise \(^{(17)}\).

**Figure 34: Cori cycle**

*Figure 34: Cori cycle*

**5.4: LACTATE SHUTTLE: BLOOD LACTATE AS AN ENERGY SOURCE.**

Isotope tracer studies show that lactate produced in fast-twitch muscle fibers (and other tissues) circulates to other fast-twitch or slow twitch muscle fiber for conversion to pyruvate. Pyruvate in turn, converts to acetyl-CoA for entry into citric acid cycle for aerobic energy metabolism. This process of lactate shuttling among cells enables glycogenolysis in one cell to supply other cells with fuel for oxidation \(^{(17)}\).

**5.5: ONSET OF BLOOD LACTATE ACCUMULATION:**

During low-intensity, steady-rate exercise, blood lactate concentration does not increase beyond normal biologic variation observed at rest. As exercise intensity increases, blood lactate level exceed normal variation. Exercise intensity associated with a fixed
blood lactate concentration that exceeds normal resting variation denotes the LT. This often coincides with a 2.5 milimoles (mM) value. A 4.0 mM lactate value indicates the onset of blood lactate accumulation (OBLA)\(^{(17)}\).

An increased blood lactate concentration is common during physiological (exercise) and pathophysiological stress (stress hyperlactataemia). In disease states, there is overwhelming evidence that stress hyperlactataemia is a strong independent predictor of mortality. However, the source, biochemistry, and physiology of exercise-induced and disease-associated stress hyperlactataemia are controversial. The dominant paradigm suggests that an increased lactate concentration is secondary to anaerobic glycolysis induced by tissue hypo perfusion, hypoxia, or both\(^{(98)}\).

The normal plasma lactate concentration is 0.3–2.3 mmol/L. Considered once as a special investigation; it is increasingly measured automatically with the blood gas analysis. Plasma concentrations represent a balance between lactate production and lactate metabolism. In humans, lactate exists in the levorotatory isoform. Normal lactate production Glycolysis in the cytoplasm produces the intermediate metabolite pyruvate.

Under aerobic conditions, pyruvate is converted to acetyl CoA to enter the Kreb’s cycle. Under anaerobic conditions, pyruvate is converted by lactate dehydrogenase (LDH) to lactic acid. In aqueous solutions, lactic acid dissociates almost completely to lactate and H\(^+\) (pKa at 7.4 \(\approx\) 3.9) which is shown in figure 32. Consequently, the terms lactic acid and lactate are used somewhat interchangeably. Lactate is buffered in plasma by NaHCO\(_3\)\(^{(97)}\).

Strength exercises are usually characterized by high energy demand and restricted blood flow during time under tension (TUT).
Thus, due to the hypoxic environment experienced by the exercising muscle, anaerobic energy metabolism plays an important role during resistance exercise. As a result, lactate production is increased in the working muscles, especially in type II muscle fibers, and consequently blood lactate concentration [La] increases. [La] depends on production, transportation, metabolism, and elimination of lactate and is commonly used to estimate lactate production/elimination in muscle (Beneke et al., 2011; Dotan, 2012)\(^{(99)}\).

5.6: BLOOD LACTATE MEASUREMENT

Blood lactate concentration [La\(^{-}\)] is one of the most often measured parameters during clinical exercise testing as well as during performance testing of athletes. Because measurements of an elevated [La\(^{-}\)] may be used to evaluate an underlying pathology during a routine stress test (coronary artery disease, chronic airway obstruction, chronic renal failure, metabolic impairment), and also to prescribe appropriate exercise intensities for different patient populations, it has been recommended that [La\(^{-}\)] analysis be added to normal stress testing measurements \(^{(100)}\).