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An Investigation of Glycolysis, Metabolic Acidosis, and Lactate's Role in Cellular Respiration

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### Abstract

Distance runners and coaches, when discussing fatigue and soreness after a competition and intense training, typically blame lactic acid. Most often the origins of these beliefs have been handed down to the coach or athlete by their coach, who heard it from their coach, and so on. In that respect, the notion that lactic acid was the cause of the aftereffects of intense physical activity was accurate, based on the knowledge available when the theories were created in 1922 by Meyerhoff and Hill who won the Nobel Prize for their discoveries. However, over the last century, advancements in research have found that the theories of the time were not entirely accurate. In an attempt to clear up the rumors that surround lactic acid, an introductory discussion describing cellular energy and its modes of production, followed by a clarification of glycolysis and lactate production, will lead into the explanation of ATP hydrolysis resulting in metabolic acidosis. Afterward, the topics including details about the buffering of the cellular environment and lactate removal, and the descriptions of assessments that measure the amount of lactate buildup will conclude with the importance of training to improve the effects of lactate accumulation.

### An Investigation of Glycolysis, Metabolic Acidosis, and Lactate's Role in Cellular Respiration

Leading up to his appearance in the 1972 Munich Olympic Games, Steve Prefontaine was quoted in *Sports Illustrated* as saying “A lot of people run a race to see who is fastest. I run to see who has the most guts, who can punish himself into an exhausting pace, and then at the end who can punish himself even more” (Putnam, 1972, p.36). When Prefontaine made this statement, he was referring to the race strategy that would hopefully earn him an Olympic Gold Medal in the men's 5000 meters. Prefontaine went on to explain his race strategy as “Nobody is going to win the gold medal after running an easy first two miles. Not with me. If I lose forcing the pace all the way, well, at least I can live with myself. But if it's a slow pace, and I get beaten by a kicker who leaches off the front, then I'll always wonder, ‘What if...?’ Right now I'd say we'd go out in world record pace for the first couple miles, and then I'll turn it on, start destroying people. If anyone wants to beat me, let them run a world record” (Putnam, 1972, p.36). At the time, the world record time of 13:16.6, resulting in a pace of 4:16 minutes per mile, in the men's 5000 meters was held by Ron Clarke of Australia (International Association of Athletics Federations [IAAF], 2017). Prefontaine's goals for Olympic gold were attainable because, in order to qualify for the 1972 Olympic Games during the American Olympic Qualifying Trials held in Eugene, Oregon, Prefontaine set the American record for the 5000 meters by running a time of 13:22.8, which included a split of 4:07.8 for his last mile (Amdur, 1972).

As the Olympic games approached, Prefontaine's training was on pace to achieve his goals with interval training sessions completed at goal paces and total running mileage approaching 100 miles per week (Amdur, 1972) In the 1972 New York Times Article “Prefontaine Is Heading For The Last Lap-Munich” written by Neil Amdur, an example of the interval training that Prefontaine was completing was given and included three 1200 meter

repeats (3:11, 3:07, 3:01), nine 300 meter repeats (0:48, 0:48, 0:48, 0:45, 0:45, 0:45, 0:44, 0:43, 0:40), and four 100 meter sprints with “brief jogs” serving as recovery.

Unfortunately, Prefontaine’s race strategy and planning would not pay off during the Olympic men’s 5000 meters. Contrary to Prefontaine’s prediction, the field did not begin the race at a world record pace, which would result in a time around 8:32 or less for the first two miles. Instead of the faster world record breaking race that Prefontaine had hoped for, the split for the first two miles was much slower with a time of 8:52 (Newnham, 1972). Entering the final mile of the race, Prefontaine surged and led the race for the first 800 meters in an attempt to take control of the race and set up for the type of finish that he had been training for (Newnham, 1972). Entering the final 800 meters of the race, Lasse Viren of Finland surged ahead of Prefontaine to take the lead, and the final battle for an Olympic Medal began and also included the runners Emiel Puttemans of Belgium, Ian Stewart of Great Britain, and Mohamed Gammoudi of Turkey (Newnham, 1972). With 700 meters to go, Prefontaine who had quickly fallen to fourth in the field, and who was trailing the lead runner Viren by approximately 5 meters, began a significant increase of his already fast pace in an attempt to regain the lead (Wijaya, 2014). Entering the final 500 meters of the race, Prefontaine had not only surged ahead to take the lead but was approximately three meters ahead of Viren who was second (Wijaya, 2014). As the final 400 meters began, Viren and Gammoudi, who had stayed manageably close to Prefontaine during his earlier 200-meter surge, began their finishing kicks and Prefontaine quickly fell to third with 300 meters to go (Wijaya, 2014). Prefontaine surged one last time with 300 meters to go and moved into a position even with Viren and Gammoudi (Wijaya, 2014). However, with 150 meters left in the race, Prefontaine was not capable of maintaining the race pace and quickly fell behind Gammoudi and Viren who had surged ahead to gain an approximate 15 meter lead on

Prefontaine (Wijaya, 2014). As Prefontaine approached the finish line with 30 meters to go, the effects of the grueling race were apparent as he was passed by Ian Stuart of Great Britain and was denied the opportunity of winning an Olympic medal as he finished fourth overall with a time of 13.26.4 (Wijaya, 2014). During the post-race interview, Prefontaine explained how he felt during the final stretch of the race by stating “I didn’t have anything left the last 50 meters and that means I ran a hard mile. I made those son-of-a-guns run that last mile. Maybe I could have run a faster time if I’d held back, but I was running to win” (Newnham, 1972, p. 3B).

Considering the post-race comments made by Prefontaine along with the accounts of what points, and to what intensity, during the last 800 meters he began his kick. One can suggest that Prefontaine started his finishing kick too early, or too fast when he surged ahead of the field by five meters with nearly a lap and a half to go in the race. Steve Prefontaine, whose aerobic capacity equated to a  $VO_{2max}$  of 84.4 ml/kg/min, was capable of performances that ranks him as one of the most iconic distance runners in American history (Noakes, 2002). However, during Prefontaine’s early finishing kick, metabolic acidosis and the effects that it has on the human body may have been a significant contributing factor to Prefontaine not having “anything left” at the end of the men’s 1972 Olympic 5000 meters.

The lactate threshold or metabolic acidosis is a phenomenon that most everyone has experienced at one point in their lives and is not a process reserved for those distance runners engaged in intense training regimens and competition such as Steve Prefontaine. These individuals include the middle schooler who is going to attempt to win the one mile run for gym class in the first 300 meters, or the sedentary individual whose new year’s resolution is to run 3 miles on January 1 but ends up running the first half mile and walking the rest. Among some distance runners and coaches, the concept of lactate production and its role in training and

recovery is profoundly misunderstood, however, after understanding the process of metabolic acidosis and the reason for lactate's production, accumulation, and role in cellular respiration, athletes and coaches can design training programs that improve athletic performance.

### **Cellular Energy and Modes of Production**

The purpose of cellular respiration, in skeletal muscle tissue, is to create the chemical energy needed to carry out the muscular contractions that result in movements such as running (McArdle et al., 2010). The chemical energy used by muscle tissue is provided by the molecule adenosine triphosphate (ATP) (McArdle et al., 2010). The adenosine portion of ATP consists of one molecule of the monosaccharide ribose linked to a molecule of adenine, while the triphosphate portion of ATP contains a chain of three phosphate group molecules consisting of phosphorous and oxygen (McArdle et al., 2010). The chemical bonds that link the first phosphate group to the second group, and which connect the second phosphate group to the third contain a high amount of chemical energy that is released when ATP joins with water in a process called hydrolysis (McArdle et al., 2010). During hydrolysis, the reaction of water and ATP is catalyzed by the enzyme adenosine triphosphatase (ATPase) which results in the release of one inorganic phosphate group from the ATP molecule and a positively charged hydrogen ion (Haff & Triplett, 2016). Furthermore, this reaction results in a molecule of adenosine diphosphate (ADP) and the release of 7.3 kCal of free energy (McArdle et al., 2010). Occasionally, further hydrolysis of the ADP molecule can occur through a catalyzing reaction involving ATPase, where the second inorganic phosphate group is cleaved from ADP, resulting in a molecule of adenosine monophosphate (AMP), a positively charged hydrogen ion, and the release of additional energy (Haff & Triplett, 2016; McArdle et al., 2010).

Skeletal muscles cells contain a small amount of ATP that is readily available (McArdle et al., 2010). However, as energy requirements increases, so does the production of ATP so that amounts of available energy never decrease within the cell (McArdle et al., 2010). To create this additional ATP, skeletal muscle cells rely on the breakdown of macronutrients found in foods which include carbohydrates, fats, and proteins (McArdle et al., 2010). Chemical breakdown of these larger food macronutrient molecules, through the processes of digestion and absorption, results in the substrates of simple carbohydrates, fatty acids, and amino acids (McArdle et al., 2010). Once absorbed by the body, these smaller molecules of simple carbohydrates, fatty acids, and amino acids can be readily absorbed by cells to fuel cellular respiration or, through a process called glycogenesis, stored as glycogen in the liver and muscle cells or stored as fat in adipose tissue (McArdle et al., 2010). However, with one molecule of glucose yielding 32 ATP molecules and one triglyceride molecule creating 460 ATP molecules, triglyceride fatty acids and the simple carbohydrate glucose are the preferred substrates utilized by cellular respiration (McArdle et al., 2010).

Once these micronutrients are available to skeletal muscle cells, within the cell's cytoplasm, the two processes of the phosphagen and the glycolytic systems along with the oxidative system, located within the mitochondria of the cell, synthesize ATP (Haff & Triplett, 2016; McArdle et al., 2010). Depending on the intensity of the activity, specific energy systems are utilized more than others to produce ATP, however, all energy systems contribute to the production of ATP at all times (Haff & Triplett, 2016). During short and explosive activities lasting 6 seconds, such as a 60-meter sprint, the primary energy system utilized is the phosphagen system which uses hydrolysis to release the high energy bonds found in limited amounts of phosphocreatine (PCr) to resynthesize ADP into ATP (McArdle et al., 2010). For



activities of very high intensity lasting between six to 30 seconds, such as a 200-meter sprint, the primary energy systems used are both the phosphagen and fast glycolysis system which results in the production of lactate as an end product (Haff & Triplett, 2016). Those activities of high intensity, lasting between 30 seconds and two minutes, such as a 400-meter run, a 800-meter run, or the final kick during the last few hundred yards of a mile run, primarily rely on the fast glycolysis system which results in lactate production (Haff & Triplett, 2016; McArdle et al., 2010). During moderate intensity activities lasting between 2 minutes and 3 minutes, the enzyme activity of the mitochondria can manage pyruvate production resulting from fast glycolysis for a short time, however, once the pyruvate production exceeds what the mitochondria can manage, pyruvate is converted into lactate (Haff & Triplett, 2016). Lastly, during low-intensity activities, such as walking longer than three minutes, the slower processes of the oxidative system, including the Krebs's cycle and electron transport, can manage slow glycolysis pyruvate production without producing substantial amounts of lactate (Haff & Triplett, 2016). Furthermore, during light to moderate physical activity, fatty acids are the primary substrate source for slow glycolysis and the oxidative system, including the Krebs cycle and electron transport, with the breakdown of glucose only contributing one-third of the need (McArdle et al., 2010). However, as physical activity intensity increases, glucose becomes predominate as a fuel source for ATP production as it is the only substrate utilized during anaerobic conditions (McArdle et al., 2010).

### **Glycolysis and Lactate Production in Depth**

The word glycolysis originates from the Greek language and translates into “the dissolution of sugar” (McArdle et al., 2010). Berg, Tymoczko, & Stryer (2002) explain the process of glycolysis as “the sequence of reactions that metabolizes one molecule of glucose into

two molecules of pyruvate with the concomitant net production of two molecules of ATP” (p. 425). When life on earth was in its infancy, glycolysis was one of the earliest forms of energy production enabled by microorganisms (Berg et al., 2002). It is believed that glycolysis, which does not rely on oxygen, was relied upon by these organisms because amounts of earth’s atmospheric oxygen were low at the time (Berg et al., 2002). Furthermore, the violent environmental conditions of early earth allowed for the creation of glucose from atmospheric formaldehyde which could then be used to fuel the anaerobic metabolism for early life (Berg et al., 2002). Single-celled organisms, such as some bacteria and yeasts, still rely on anaerobic glycolysis to metabolically turn glucose into ethanol through alcoholic fermentation (Berg et al., 2002). However, the processes of activity-dependent anaerobiosis, which has evolved in species such as humans and other mammals, allows for glycolysis to be used in aerobic conditions, which turns glucose into pyruvate to further fuel oxidative phosphorylation, or during anaerobic conditions, where glycolysis is able to continually produce ATP through the production of lactate (McArdle et al., 2010).

The ten step process of anaerobic fast glycolysis, resulting in lactate production, begins when a molecule of glucose enters the cell’s cytoplasm through glucose transport proteins (GLUT) found on the cell’s plasma membrane (Berg et al., 2002). There are five types of GLUT proteins respectively named GLUT1 through GLUT5, with GLUT1, GLUT3, and GLUT4 being responsible for glucose uptake in muscle and fat cells (Berg et al., 2002). Through passive transport, GLUT1 and GLUT3 supply the cells with a constant supply of glucose where GLUT4 proteins increase in number due to a hormonal response of insulin presence (Berg et al., 2002).

The first step of glycolysis occurs immediately after the glucose molecule is inside of the cell, it is phosphorylated by the enzyme hexokinase through the expenditure of one molecule of

ATP (Berg et al., 2002). This reaction results in a molecule of glucose 6-phosphate, a molecule of ADP, and one positively charged hydrogen ion (Berg et al., 2002). The purpose of this reaction is to alter the chemical structure of glucose so it cannot leave the cell through the GLUT proteins, and to prepare the cell for the next step of glycolysis that relies on destabilization of the glucose molecule (Berg et al., 2002). However, this step can be skipped, and the molecule of ATP saved if the glucose is removed from a molecule of glycogen, which is phosphorylated by the enzyme phosphorylase, resulting in the desired molecule of glucose 6-phosphate (McArdle et al., 2010).

During the second step, once the stable glucose molecule is phosphorylated into the less stable glucose 6-phosphate, the enzyme phosphoglucose isomerase changes the molecular structure into a molecule of fructose 6-phosphate (Berg et al., 2002). The enzyme phosphoglucose isomerase opens the six-membered ring of glucose 6-phosphate and, through a rearrangement of atoms called an isomerization, creates an open form of the molecule fructose 6-phosphate which is then closed, resulting in a five-membered ring molecule (Berg et al., 2002).

The third step requires another molecule of ATP to be spent when, the rate-limiting enzyme phosphofructokinase (PFK) phosphorylates fructose 6-phosphate, which results in a molecule of fructose 1,6-biphosphate, a molecule of ADP, and another positive hydrogen ion (Berg et al., 2002). PFK acts as the rate-limiting enzyme in glycolysis because of its sensitivity of increasing acidity in the cytosol of the cell that inhibits the enzyme from continuing glycolysis (Berg et al., 2002). Additionally, PFK is a rate limiting enzyme because of its sensitivity to ATP, which can bind to sites on PFK that inhibits the enzyme's activity during glycolysis (Berg et al., 2002). Furthermore, molecules of AMP can also bind to the enzyme, which results in PFK increasing activity based on the lower amounts of chemical energy available in the cell (Berg et al., 2002).

In the fourth step, the enzyme aldolase splits fructose 1,6-phosphate into the two separate molecules of glyceraldehyde 3-phosphate (GAP) and dihydroxyacetone phosphate (DHAP) (Berg et al., 2002). While the molecule of GAP is chemically ready to proceed with glycolysis, the DHAP molecule requires isomerization completed by the enzyme triose phosphate isomerase, which results in a molecule of GAP (Berg et al., 2002). Once the DHAP molecule has been isomerized into GAP, the overall splitting of fructose 1,6-phosphate results in two individual molecules of GAP that proceed through glycolysis individually following a different but similar path (Berg et al., 2002).

The fifth step of glycolysis involves the dehydrogenase enzyme named nicotinamide adenine dinucleotide (NAD<sup>+</sup>) and the enzyme glyceraldehyde 3-phosphate dehydrogenase that chemically changes the GAP molecule into a molecule of 1,3-biphosphoglycerate, the reduced NADH, and another positive hydrogen ion (Berg et al., 2002). After this reaction, under high-intensity conditions with less oxygen being delivered to the cell, the molecule 1,3-biphosphoglycerate continues through with glycolysis while the NADH molecules begin to accumulate within the cytoplasm, awaiting pyruvate, the end product of glycolysis (Berg et al., 2002).

During the sixth through the ninth step of glycolysis, after the formation of 1, 3-biphosphoglycerate, the enzyme phosphoglycerate kinase uses substrate-level phosphorylation to create one molecule of ATP and a molecule of 3-phosphoglycerate (Berg et al., 2002). Overall, due to the splitting of fructose 1,6-phosphate in step four, this reaction accounts for a total production of two ATP molecules. Next, the enzyme phosphoglycerate mutase reconfigures the molecule of 3-phosphoglycerate to create a molecule of 2-phosphoglycerate (Berg et al., 2002). Afterward, the enzyme enolase catalyzes the reaction that changes 2-phosphoglycerate into a

molecule of water and a molecule of phosphoenolpyruvate (Berg et al., 2002). Then, in the ninth step of glycolysis, another molecule of ATP is created when the enzyme pyruvate kinase catalyzes the molecule phosphoenolpyruvate, a positive hydrogen ion, and a molecule of ADP into a molecule of pyruvate (Berg et al., 2002; Busa & Nuccitelli, 1984). As mentioned previously, due to the splitting of fructose 1,6-phosphate in step four, this reaction accounts for a production total of four ATP molecules. However, because two ATP molecules were invested during the first and third step of glycolysis, the net result of ATP production during the entire anaerobic glycolytic pathway is two ATP, or three ATP if the glucose originated from intracellular glycogen.

The final step in lactate production during fast glycolysis involves the NADH enzymes that have accumulated in the cytosol of the cell after the fifth step of glycolysis, where  $\text{NAD}^+$  is required for the production of 1,3-biphosphoglycerate. This accumulation is more due to a production of NADH that is too rapid for the oxidative system to handle than the lack of available oxygen (Berg et al., 2002; McArdle et al., 2010). For glycolysis to continue, the accumulating NADH enzymes need to be oxidized back to their  $\text{NAD}^+$  form so that the production of 1,3-biphosphoglycerate can continue (Berg et al., 2002; McArdle et al., 2010). The needed replenishment of  $\text{NAD}^+$  occurs when the enzyme lactate dehydrogenase, along with the addition of another positive hydrogen ion, reduces pyruvate into lactate by oxidizing NADH into  $\text{NAD}^+$  (Berg et al., 2002; McArdle et al., 2010).

In summary, after evaluation of the entire process of anaerobic glycolysis, when glycolysis begins with glucose, four positive hydrogen ions are released which includes one during step one, another in step three, and two more during step five of each glycolytic pathway (Busa & Nuccitelli, 1984). However, during the ninth and tenth steps, which results in two

pyruvate molecules and two lactate molecules respectively, four positive hydrogen ions are consumed resulting in no accumulation of positive hydrogen ions (Busa & Nuccitelli, 1984). Furthermore, if glycolysis begins with glucose from glycogen, only three positive hydrogen ions are produced in steps three and five, while four positive hydrogen ions are consumed in steps nine and ten resulting in an alkalization of the cellular environment (Busa & Nuccitelli, 1984). Therefore, since lactate is the end product of fast glycolysis, the misconceptions of distance runners and coaches involving the effects of lactic acid while running at high intensities is invalidated. Moreover, after accounting for the positive hydrogen ions released and consumed during glycolysis resulting in lactate production, it is further contradicted that the process of anaerobic glycolysis, that consumes protons in the creation of lactate, contributes to the acidity of the cellular environment.

#### **ATP Hydrolysis Resulting in Metabolic Acidosis**

During muscular contractions utilizing the enzyme myosin ATPase, the hydrolysis of ATP results in the chemical energy that causes the power-stroke between myosin and actin which shortens muscle sarcomeres. (Haff & Triplett, 2016). Additionally, with the production of chemical energy, the products of the hydrolyzing of the ATP molecule result in a molecule of ADP, an inorganic phosphate group, and a positive hydrogen ion (Robergs, Ghiasvand, & Parker, 2004). Under running and exercise intensities that result in a steady state of ATP hydrolysis and where oxidative phosphorylation is utilized, the resulting positive hydrogen ion, inorganic phosphate, and ADP molecule are used by the mitochondria to regenerate ATP (Robergs et al., 2004).

As stated by Robergs et al. (2004), “Metabolic acidosis occurs when the rate of ATP hydrolysis, and therefore the rate of ATP demand, exceeds the rate at which ATP is produced by

the mitochondria” (p.509). Mitochondrial respiration results in the production of 0.7 mM of ATP/second/kilograms of wet muscle weight through glucose oxidation, and 0.3 mM of ATP/second/kilograms of wet muscle weight through fatty acid oxidation (Robergs, 2001). On the other hand, ATP production during the glycolytic and phosphagen system produces 1.3 and 2.4 mM of ATP/second/kilograms of wet muscle weight respectively (Robergs, 2001). When running and exercise intensities increase beyond the steady state, and the rate that active muscles hydrolyze ATP exceeds the rate of its production from mitochondrial respiration, the rate of glycolytic reactions increases to compensate for the limitations of the mitochondrial production of ATP (Robergs, 2001). As the rate of glycolysis increases, amounts of pyruvate produced exceeds the rate that the mitochondria can consume, and pyruvate accumulates in the cytosol of the cell and within the mitochondria (Robergs, 2001). Since the transformation of lactate from pyruvate relies on the enzyme lactate dehydrogenase and NADH, there are limitations to the amounts of lactate that can be formed from pyruvate when pyruvate is being produced too rapidly (Robergs, 2001). When the rate of lactate formation exceeds pyruvate creation, continued hydrolysis of ATP of working muscles causes positive hydrogen ions to accumulate along with NADH from glycolysis (Robergs, 2001). The effects of the accumulation cause a decrease in pH of the cellular environment causing metabolic acidosis, inactivates glycolytic enzymes such as PFK, impairs muscle contraction, and creates the burning sensation in working muscles (McArdle et al., 2010; Robergs, 2001).

When evaluating the positive hydrogen ion balance during three minutes of intense exercise to fatigue, the phosphagen system produces an accumulation of 70 mM/ kilograms of wet muscle weight of positive hydrogen ions during ATP hydrolysis while a depletion of 20 mM/ kilograms of wet muscle weight of hydrogen ions occurs during the rebuilding of ATP

(Robergs, 2001). In addition, the process of glycolysis produces 65 mM/ kilograms of wet muscle weight of hydrogen ions during the production of glucose 6-phosphate, 65 mM/ kilograms of wet muscle weight of hydrogen ions during the production of fructose 1,6 bisphosphate, and 130 mM/ kilograms of wet muscle weight of hydrogen ions during the production of 1,3-bisphosphoglycerate (Robergs, 2001). The consumption of hydrogen ions during glycolysis occurs when 130 mM/ kilograms of wet muscle weight of hydrogen ions are used to create pyruvate and when 30 mM/ kilograms of wet muscle weight of hydrogen ions are used during the creation of lactate (Robergs, 2001).

Overall, positive hydrogen ion production compared to consumption results in 330 mM/ kilograms of wet muscle weight of hydrogen ions produced compared to 180 mM/ kilograms of wet muscle weight of hydrogen ions consumed (Robergs, 2001). What is important to note considering this evaluation of mM/ kilograms of wet muscle weight of hydrogen ions produced and consumed during three minutes of intense exercise to exhaustion, is that the hydrogen ions are products from reactions that require ATP hydrolysis. Also, it is important to take notice that the reaction resulting in lactate from pyruvate consumes hydrogen ions and does not release them thus, contributing to the buffering of the cellular environment and not causing acidosis.

### **Buffering Of the Cellular Environment and Lactate Removal**

Metabolic acidosis is not only caused by the production and accumulation of positive hydrogen ions in the cell but, is the result of an imbalance of the rate of ion buffering within the cell, ion elimination from the cellular environment, and ion buffering through blood and ventilation (Robergs et al., 2004). As positive hydrogen ions accumulate within the cell, buffering of the cellular environment occurs through ion binding capabilities of proteins and amino acids within the cytosol, lactate production, and ATP creation by the phosphagen system



(Robergs et al., 2004). Additionally, positive hydrogen ions are removed from the cellular environment through mitochondrial oxidation, removal of lactate through monocarboxylate transporters, and sodium-hydrogen exchanges located on the plasma membrane (Robergs et al., 2004). Blood and ventilatory buffering of positive hydrogen ions occur as a result of the carotid chemoreceptors response to changes in blood pH that initiates increased respiration (McArdle et al., 2010). As blood plasma pH decreases, positive hydrogen ions bind to molecules of bicarbonate to form molecules of carbonic acid, which are then dissociated into a molecule of water and a molecule of carbon dioxide, which is then exhaled (McArdle et al., 2010).

As described earlier, the positive hydrogen ions that are removed from the cellular environment, through monocarboxylate transporters, are attached to molecules of pyruvate resulting in molecules of lactate. As a result, when running intensity increases, the amount of lactate levels in the blood increases due to the increased rate of carbohydrates being processed by glycolysis, that results in increased amounts of positive hydrogen ions in the blood, which causes a decrease in blood pH (Noakes, 2002; Robergs et al., 2004). Therefore, lactate gets a “bad name” because of its association with these positive hydrogen ions and results in additional misconceptions about lactate that are shared among some distance runners and coaches. A few of these other misconceptions include the belief that lactate is a negative byproduct of high-intensity running and is the cause for soreness days following intense training or races. To begin, the negative connotation that lactate has developed, among some runners and coaches, as a wasteful negative byproduct of metabolism, could not be further from the truth because lactate’s role in cellular respiration is to provide additional energy for muscle function (McArdle et al., 2010).

As exercise intensity in previously active muscle decreases and the cellular environment moves towards a steady state, mitochondrial respiration begins to oxidize excess positive hydrogen ions that are available within the cell that include those connected to the molecules of pyruvate during the formation of lactate (McArdle et al., 2010). In a near reversal of the pyruvate into lactate reaction, available  $\text{NAD}^+$  enzymes remove the hydrogen ions from molecules of lactate to become  $\text{NADH}$  and transport them into the mitochondria for oxidation (McArdle et al., 2010). The dismemberment of hydrogen ions by  $\text{NAD}^+$ , from lactate molecules, result in a molecule of pyruvate that is allowed to enter the mitochondria to produce ATP, or transformed into glucose by gluconeogenesis (Berg et al., 2002).

Additionally, lactate produced in active cells can be added to the exchangeable lactate pool and utilized by other cells through the process of lactate shuttling (McArdle et al., 2010). Doctor Timothy Noakes (2002), describes the lactate shuttle as “a convenient method by which body carbohydrate stores can be redistributed from glycogen-replete areas to glycogen-depleted areas during and especially after exercise” (p. 163). One way that the lactate shuttle contributes to the redistribution of energy stores between muscle cells occurs when lesser active muscle cells convert available glycogen supplies into lactate during periods of intense running that are greater than 80% of an individual’s aerobic capacity (McArdle et al., 2010). The lactate produced by the lesser active muscle cells becomes part of the exchangeable lactate pool, and is transported to active muscle tissues through the bloodstream where it is changed back into pyruvate and then, oxidized in the mitochondria for ATP production (McArdle et al., 2010). On the other hand, excess lactate that is produced during intense activity by muscle tissues with less oxidizing ability, such as Type II muscle tissues, is transferred to neighboring muscle cells with more

oxidizing capacity, such as Type I muscle tissues, where it is then converted back into pyruvate for energy production or stored as glycogen (McArdle et al., 2010).

The organs of the heart and liver also play essential roles in the removal of lactate from the blood during times of exercise and rest (Noakes, 2002). During times of intense running or other physical activity, the cardiac muscle cells of the heart utilize circulating lactate available in the bloodstream more than circulating glucose for the mitochondrial generation of ATP (Chatham, 2002). Due to the heart's abundant supply of oxygenated blood, molecules of lactate which are readily permeable to the plasma membranes of cardiac muscle cells because of specific carriers, are quickly converted to pyruvate for mitochondrial energy production (Berg et al., 2002). Lastly, the liver removes the excess amounts of lactate in the bloodstream which it converts into pyruvate and then, into glucose through the process of gluconeogenesis (Berg et al., 2002). Once the liver has converted lactate into glucose, the glucose reenters the bloodstream to fuel continued muscle activity or is stored within the liver as glycogen (McArdle et al., 2010). The liver's resynthesis of lactate into glucose can be seen as the final step of the Cori Cycle, or the cycling process of the liver creating glucose for active muscles, which is then converted into lactate by active muscles, which is then resynthesized into glucose by the liver (Berg et al., 2002).

In summary, lactate is not the wasteful negative by-product that it is believed to be by some distance runners and coaches but, instead, an essential role in energy metabolism that "buys time and shifts part of the metabolic burden from muscle to other organs" (Berg et al., p. 458, 2002). After exercise intensities that cause the "metabolic burden", the accumulations of lactate diminish to normal values within an hour due to quick reconversion of lactate into the useable ATP substrates of pyruvate, glucose, or glycogen (Noakes, 2002). Therefore, the other

misconception shared among some distance runners and coaches regarding lactate remaining in active muscle tissues and causing muscle cramps and stiffness days following intense activity is not true, and more likely due to “muscle cell damage, especially to the elastic elements in the skeletal muscles” (Noakes, p. 164, 2002).

### **Measurements of Lactate Accumulation**

During times of rest or light-to-moderate physical activity, that is less than 50% of an individual’s aerobic capacity, where slow glycolysis followed by mitochondrial respiration provides sufficient chemical energy, lactate is still produced within the body (McArdle et al., 2010). Primary contributors of constant lactate production include red blood cells, because of their inability to carry out mitochondrial respiration, and muscle fibers such as type II muscle fibers that have high glycolytic properties while lacking sufficient mitochondrial capacity for oxidation (McArdle et al., 2010). However, the lactate that is produced by these means is quickly absorbed and oxidized through lactate shuttling and does not accumulate in the blood (McArdle et al., 2010). As physical activity increases, and muscles hydrolyze more ATP, the rate of glycolysis in working muscles increases resulting in increased lactate production (Noakes, 2002). Approximately, at exercise intensities of greater than 50% of aerobic capacity for untrained individuals, or between 80-90% for endurance trained athletes, the rate of lactate production begins to exceed the rate that lactate is processed by the liver, heart, and other muscle tissues and begins to accumulate in the blood (McArdle et al., 2010).

Traditional methods that measure an individual’s level of cardiovascular fitness, based on blood lactate accumulation, can be determined through data collected by blood draws during submaximal or maximal fitness assessments. During the assessment, while engaged in light to moderate running or exercise, there are increases of lactate in the blood that measure less than

one mM per individual measurement (McArdle et al., 2010). As running or exercise intensity increases, the exercise intensity when the individual's blood lactate increases more than one mM for a single measurement, represent the individual's lactate threshold, or the first sign of "anaerobic muscular activity" (McArdle et al., 2010; Noakes, 2002). Furthermore, as running or exercise intensity increases and total blood lactate measurements reach four mM, the corresponding intensity of running or exercise represents an individual's onset of blood lactate and is believed, by some, to represent the intensity when active muscles become "mostly anaerobic" (McArdle et al., 2010).

Also, an individual's cardiovascular fitness and the onset of blood lactate accumulation can be assessed through changes in ventilation due to positive hydrogen ions within the blood (McArdle et al., 2010). During light to moderate running or exercise, an individual's ventilatory equivalent, or the ratio of an individual's minute ventilation, or total gas volume inhaled and exhaled, compared to the amount of oxygen consumed and carbon dioxide produced, follows a linear pattern (McArdle et al., 2010). However, the exercise intensity when the individual's ventilatory equivalent increases, compared to oxygen consumption, and deviates from the linear pattern indicates the individual's ventilatory threshold (McArdle et al., 2010). The physiological processes indicated by the ventilatory threshold is the need to expel additional amounts of carbon dioxide, as the result of the buffering of excess positive hydrogen ions in the blood with lactate, which then creates the increase in minute ventilation compared to oxygen consumption (McArdle et al., 2010).

These prior methods of blood lactate accumulation monitoring were created with the generalized foundational principles of the era that included the role of lactate being what causes muscle contraction and the belief that muscles functioned anaerobically during periods of intense

physical activity (Noakes, 2002). Research over the century has shed light on these generalized foundational principles and questioned their validity due to gained knowledge of muscles producing lactate while fully oxygenated, muscles never becoming anaerobic at any intensity of physical activity, or the process of lactic shuttling (Noakes, 2002). Therefore, alternate methods that measure blood lactate have been developed based on the current knowledge available to the scientific community. Such a technique currently adapted to the current understanding of lactate and its accumulation is maximal lactate steady state which is “considered the gold standard endurance performance marker among the vast majority of sport and exercise physiologists” (Garcia-Tabar & Gorostiaga, p. 2, 2018). The foundation of maximal lactate steady state is based upon an individual’s metabolic and respiratory response to four intensities of exercise (Smith, & Jones, 2001) First, during moderate intensity of exercise, an exponential rise in oxygen uptake occurs until a steady state is reached that is matched with a slight rise in blood lactate that returns to pre-exercise levels (Smith, & Jones, 2001). Next, during heavy exercise levels, exercise levels increase until blood lactate levels reach a steady state (Smith, & Jones, 2001). Very heavy exercise is characterized by a continual increase in oxygen consumption and blood lactate until exercise ends (Smith, & Jones, 2001). Lastly, severe exercise is represented by exponential increases in oxygen consumption to maximal levels and steep rises in blood lactate levels until fatigue (Smith, & Jones, 2001). Therefore, the measurement of an individual’s maximal lactate steady state refers to the intensity of exercise where lactate accumulation matches lactate removal or the intensity of exercise that separates heavy exercise from very heavy exercise (Smith, & Jones, 2001; Almarwaey, Jones, & Tolfrey, 2004).

An example of a maximal lactate steady state assessment can include a progressive maximal assessment where blood lactate draws are taken after each stage that includes increases

in running speed of one km/hour that are three minutes in duration (Almarwaey et al., 2004). Afterward, calculations of the individual's specific running speed are made based on the measured blood lactate concentration during the progressive maximal test (Noakes, 2002). For example, calculated running speeds can include multiple running speeds to be tested based on whole number blood lactate concentrations such as two mM/liter, three mM/liter and four mM/liter resulting in running speeds of 17 km/hr., 18 km/hr., and 19 km/hr. (Noakes, 2002). Next, on separate days, the runner runs for 25 minutes at each of the calculated running speeds and blood lactate measurements are taken every five minutes (Noakes, 2002). The calculated running speed where lactate measurements do not increase or decrease is then considered the maximal lactate steady state (Noakes, 2002). Based on the presented example, if lactate levels fall while running 17 km/hr. and rise while running 19 km/hr. but stay steady while running 18 km/hr.; the individual's maximal lactate state is, therefore, 3 Mm/liter and a running speed of 18 km/hr. (Noakes, 2002). In summary, an assessment of an individual's maximal lactate steady state is very time-consuming due to the multiple days needed for testing (Smith, & Jones, 2001). However, the method is recommended "where precision is needed in exercise testing or prescription, and in experimental studies" (Smith, & Jones, 2001).

### **Training to Improve Effects of Lactate Accumulation**

For endurance athletes and their coaches, the importance of understanding at what exercise intensity the lactate threshold, ventilatory threshold, or maximal lactate steady state occurs gives the athlete or coach a standard for the intensity of exercise prescriptions. For athletes who regularly train at, or above, their lactate threshold or maximal lactate steady state, cellular adaptations occur, due to the principle of progressive overload, that result in faster running intensities at the maximal lactate steady state, lactate threshold, or ventilatory threshold

as a result of improvements in  $VO_{2max}$ ,  $\%VO_{2max}$ , or running economy (McArdle et al., 2010; Enoksen, Shalfawi, & Tønnessen, 2011).

Examples of cellular and biochemical adaptations that occur due to regular training at or above the maximal lactate steady state include increases in the size and number of mitochondria in the muscle cells (Holloszy & Coyle, 1984). Along with the increases in mitochondria sizes and quantities, increases in mitochondrial enzymes can double or triple including the enzymes responsible for fatty acid metabolism and the enzymes responsible for NADH oxidation (Holloszy & Coyle, 1984). Glycolytic adaptations include increases in the enzyme hexokinase, that is responsible for locking glucose into the cell once it enters, and increases in GLUT 4 proteins that transport glucose across the cell's plasma membrane (Holloszy & Coyle, 1984; Berg et al., 2002). These cellular adaptations, along with increases in the number of circulatory capillaries to supply active muscles with oxygenated blood, increase the respiratory capacity of muscle cells (Holloszy & Coyle, 1984; McArdle et al., 2010). Therefore, muscle cells can produce ATP more quickly and efficiently through the utilization of fat rather than glucose, hence, delaying the onset of metabolic acidosis produced by ATP hydrolysis and lactate production (Holloszy & Coyle, 1984).

Research that has investigated training methods to increase athlete's lactate threshold velocity or maximal lactate steady state include the work of Enoksen, Shalfawi, & Tønnessen (2011) and Esfarjani & Laursen (2007). In the work of Enoksen, Shalfawi, & Tønnessen (2011), 26 well-trained middle distance runners were separated into two groups that consisted of a high-volume low-intensity group that ran 70 km/week for ten weeks and a low-volume high-intensity group that ran 50 km/week for ten weeks. Based on data collected, the researchers determined that 87-88% of  $HR_{max}$  signified an individual's lactate threshold (Enoksen et al., 2011). As a



result, low-intensity training intensity was set at 65-82% of HRmax, and high-intensity training intensity was set at 82-92% of HRmax (Enoksen et al., 2011). For six days per week, the high-volume low-intensity group trained 13% of mileage volume at 82-92% of HRmax, 87% at 65-82% of HRmax, and included one intensive workout (Enoksen et al., 2011). On the other hand, for six days per week, the low-volume high-intensity-group trained 33% of mileage volume at 82-92% of HRmax, 67% at 65-82% of HRmax, and included three intensive workouts (Enoksen et al., 2011). Results of the study showed that the high-intensity low-volume group increased their lactate threshold velocity from 14.6 km/hr. to 15.2 km/hr. while the low-intensity high volume group only improved from 15.3 km/hr. to 15.7 km/hr. (Enoksen et al., 2011). The relevance of this study to the topic of discussion is that the more volume of training that is dedicated to intensities at or above the lactate threshold, the better improvements in lactate threshold velocity.

In another study conducted by Esfarjani & Laursen (2007), two different high-intensity interval training (HIIT) programs were compared, and effects were tested on 3000-meter run performance. Twelve moderately trained distance runners were separated into two groups that performed their specific HIIT session twice per week for ten weeks (Esfarjani & Laursen, 2007). Group one's method of HIIT consisted of five to eight intervals ran at VO<sub>2</sub>max velocity (15.7 km/hr.) for 60% of the total time that VO<sub>2</sub>max velocity can be sustained (3.5 min) with equal work to active rest ratios (Esfarjani & Laursen, 2007). Group two's method of HIIT consisted of seven to twelve intervals ran at 130% VO<sub>2</sub>max velocity (19.9 km/hr.) for 30 seconds with 4.5-minute active recovery intervals (Esfarjani & Laursen, 2007). Results of the study showed that group one increased their lactate threshold velocity by 11.7% while group two only improved their lactate threshold velocity by 4.7% (Esfarjani & Laursen, 2007). The relevance of this study

to the topic of discussion is that a longer duration work period along with a 1:1 work to rest ratio elicits better results on lactate threshold velocity than shorter and faster work periods with longer work to rest ratios.

### **Conclusion**

In conclusion, by understanding the processes of metabolic acidosis and the reasons behind lactate's production, accumulation, and role in cellular respiration, coaches and distance runners can train more efficiently, and ultimately, perform better in competition. Steve Prefontaine and his coach Bill Bowerman understood how training above the lactate threshold enhanced endurance performance. However, just like most runners who have made the unfortunate decision to begin the race too quickly, or kick too early at the end of a race like Steve Prefontaine during the last 30 meters of the 1972 Olympic 5000 meters, have experienced, once the effects of metabolic acidosis take effect there is nothing you can do but slow down. Ultimately, after all the race preparation Prefontaine completed preparing for Munich which included 1200 meter repeats at 4:02 mile pace, and 300-meter repeats at 4:01 mile pace, all while running 100 miles/week, it was essential for Prefontaine to trust his training, and stick to his race strategy. Unfortunately though, he got caught up in the moment and deviated from his race strategy, and just like he predicted "if it's a slow pace, and I get beaten by a kicker who leaches off the front, then I'll always wonder, 'What if...?'"(Putnam, 1972, p.36).

## References

- Almarwaey, O. A., Jones, A. M., & Tolfrey, K. (2004). Maximal lactate steady state in trained adolescent runners. *Journal of sports sciences*, 22(2), 215-225.
- Amdur, N. (1972, July 30). Prefontaine Is Heading For Last Lap-Munich. Retrieved February 5, 2019, from <https://www.nytimes.com/1972/07/30/archives/prefontaine-is-heading-for-last-lap-munich.html>
- Amdur, N. (1972, July 10). U. S. 5,000 Mark Is Set By Prefontaine in Trials. Retrieved February 5, 2019, from <https://www.nytimes.com/1972/07/10/archives/u-s-5000-mark-is-set-by-prefontaine-in-trials-5000-record-set-by.html>
- Berg, J. M., Tymoczko, J. L., & Stryer, L. (2002). *Biochemistry*. New York: Freeman.
- Busa, W. B., & Nuccitelli, R. (1984). Metabolic regulation via intracellular pH. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 246(4), R409-R438.
- Butler, M. (Ed.). (2017). *IAAF World Championships London 2017 Statistics Handbook*. IAAF Communications Department.
- Chatham, J. C. (2002). Lactate—the forgotten fuel!. *The Journal of physiology*, 542(Pt 2), 333.
- Enoksen, E., Shalfawi, S. A., & Tønnessen, E. (2011). The effect of high-vs. low-intensity training on aerobic capacity in well-trained male middle-distance runners. *The Journal of Strength & Conditioning Research*, 25(3), 812-818.
- Esfarjani, F., & Laursen, P. B. (2007). Manipulating high-intensity interval training: effects on  $\dot{V}O_2\text{max}$ , the lactate threshold and 3000 m running performance in moderately trained males. *Journal of science and medicine in sport*, 10(1), 27-35.

- Garcia-Tabar, I., & Gorostiaga, E. M. (2018). A “Blood Relationship” between the Overlooked Minimum Lactate Equivalent and Maximal Lactate Steady State in Trained Runners. Back to the Old Days?. *Frontiers in physiology*, 9.
- Haff, G., & Triplett, N. T. (2016). *Essentials of strength training and conditioning*. Champaign, IL: Human Kinetics.
- Holloszy, J. O., & Coyle, E. F. (1984). Adaptations of skeletal muscle to endurance exercise and their metabolic consequences. *Journal of applied physiology*, 56(4), 831-838.
- McArdle, W. D., Katch, F. I., & Katch, V. L. (2010). *Exercise physiology: Nutrition, energy, and human performance*. Baltimore, MD: Lippincott Williams & Wilkins.
- Newnham, B. (1972, September 11). Pre's warning for 1976: 'He'd better watch out'. *Eugene Register-Guard*, p. 3B.
- Noakes, T. *Lore of Running*, 2002, Cape Town, Human Kinetics. ISBN 0-87322-959-2.
- Putnam, P. (1972, August 28). Experience May Not Be Necessary. *Experience May Not Be Necessary*, 37(9), 36. doi:<https://www.si.com/vault/1972/08/28/613155/experience-may-not-be-necessary>
- Last Name, F. M. (Year). *Book Title*. City Name: Publisher Name.
- Robergs, R. A., Ghiasvand, F., & Parker, D. (2004). Biochemistry of exercise-induced metabolic acidosis. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 287(3), R502-R516.
- Robergs, R. A. (2001). Recommendations and resources for teaching metabolic acidosis to the undergraduate student in exercise physiology. *Professionalization of Exercise Physiology*, 4.

Smith, C. G., & Jones, A. M. (2001). The relationship between critical velocity, maximal lactate steady-state velocity and lactate turnpoint velocity in runners. *European journal of applied physiology*, 85(1-2), 19-26.

Tymoczko, J. L., Berg, J. M., & Stryer, L. (2015). *Biochemistry: A short course*. New York, NY: W.H. Freeman & Company.

Wijaya, T. S. (2014, June 02). Steve Prefontaine 1972 5000m Final (English Commentary). Retrieved February 5, 2019, from [https://www.youtube.com/watch?v=\\_iKt8\\_pkHgY](https://www.youtube.com/watch?v=_iKt8_pkHgY)