EXERCISE PHYSIOLOGY AND PATHOPHYSIOLOGY OF LACTATE ACIDOSIS AND CLEARANCE

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Lactic acid is a naturally occurring molecule with original detection falling into a category of lactic acid-producing bacterial organisms. However first detected in foods, its increased concentration in muscles of hunted animals was later linked with lactate acidosis origin. Physiologically, high rate of ATP hydrolysis, occurring during anaerobic glycolysis, contributes to the formation of lactate acidosis. Not only skeletal muscles, despite of their large mass, but also brain, liver, kidney and adipose tissue function as consumers of lactate. Elevated metabolic rate during physical work promotes lactate clearance via accelerated rate of its oxidation. Strong evidence about the effects of certain diseases on lactate metabolism exists. In pathophysiology, elevated concentration of lactate in blood may be caused by its increased production, decreased clearance, or a combination of both. Abnormally increased blood lactate levels occur during hypoperfusion/hypoxemia or dysfunction of cellular metabolism. The rising body of literature demonstrating that the initial level and/or the rate of blood lactate clearance predicts the mortality following trauma, severe sepsis or cardiac surgery has accumulated.

INTRODUCTION

In sport lactate is mostly associated with intense exercises, but anaerobic glycolysis of skeletal muscle is not only producer of this metabolite. Although Lactic acid was discovered in 1780 by Swedish chemist Carl Wilhelm Scheele (Holten, Muller, & Rehbinder, 1971), Scheele detected and isolated lactic acid in samples of sour milk. The milky origin of the first discovery led to a general acceptance of a trivial name for this molecule ("lactic" - of or relating to milk). In 1856, Louis Pasteur discovered Lactobacillus and its production of lactic acid. Lately in 1907, Elie Metchnikoff hypothesized that lactic acid bacteria could normalize bowel health and prolong life. After more than half a century the term "probiotics" was coined to reflect Metchnikoff’s idea (Anukam & Reid, 2007).

The fact that lactic acid was a naturally occurring molecule with original detection in food products led to the possibility for its use in the food industry. Such intended application was aided by lactic acid’s solubility, mild acidic taste, and proven functions as a preservative. Lactic acid has been used to acidify foods and beverages, assist in the fermentation of cabbage to sauerkraut, preserve cucumbers, as an ingredient in the brewing and flavoring of beer, an ingredient to make cheese, as a source of calcium (calcium lactate) in baby food, and an ingredient in bread (Holten, et al., 1971).

A very recent research offers economical industrial production of L-lactic acid from lignocellulosic biomass (Ma, et al., 2016; Jiang, et al., 2016). In the study of Ma et al. (2016), a thermophilic strain of Bacillus coagulans was used to produce L-lactic acid from corn stover hydrolysate in membrane integrated continuous fermentation. The thermophilic strain Bacillus coagulans metabolized glucose and xylose by the Embden-Meyerhof-Parnas pathway and the pentose phosphate pathway, producing L-lactic acid with optical purity > 99.5%. Lignocellulosic biomass is a possible low-cost renewable resource of sugars for fermentation (Cardona & Sánchez, 2007; Oh, et al., 2005). Its application could not only decrease the demand for
petroleum and food raw materials but also might support the environmental demand to alleviate CO2 emissions from fossil fuels. In China, corn stover is an agricultural residue that could be used for the production of biofuel and green chemicals (Li, Lu, Zhao, & Qu, 2014).

**LACTATE AS A PRODUCT OF ANIMAL CELLS**

However, lactate acid is not produced uniquely by probiotics. Elevated lactate concentration was discovered in the muscles of hunted stags by Berzelius in 1808 (Brooks & Gladden, 2003). Early works by Hill, at the beginning of 20th century, suggested that lactate acid was the immediate energy donor for muscle contractions and Meyerhof (1920) demonstrated that glycogen was lactate’s precursor. Until the early 1970s lactate was considered a dead-end waste product of glycolysis resulting from muscle hypoxia (Wasserman, 1984). Lactic acid was also believed to be the primary cause of the slow component of the O2 debt (Margaria, Edwards, & Dill, 1933) and the major cause of muscle fatigue (Hermansen, 1981) or delayed onset muscle soreness, all of which appeared in many textbooks of biology or human physiology. As resumed in a review of Gladden (2004), the bulk of the evidence suggests that lactate is an important intermediary in numerous metabolic processes, a particularly mobile fuel for aerobic metabolism, and perhaps a mediator of redox state among various compartments both within and between cells. Lactate can no longer be considered the usual suspect for metabolic ‘crimes’, but is instead a central player in cellular, regional and whole-body metabolism. Overall, the cell-to-cell lactate shuttle has expanded far beyond its initial conception as an explanation for lactate metabolism during muscle contractions and exercise to now subsume all of the other shuttles as a grand description of the role of lactate in numerous metabolic processes and pathways.

**LACTATE ACIDOSIS**

Lactic acid is produced under basal metabolic conditions and H+ ions are released. Normally, an equivalent amount of H+ ions is consumed when the liver and renal cortex utilize for gluconeogenesis or oxidize it to water and CO2 so that acid-base balance remains undisturbed. Lactic acidosis is arbitrarily classified into overproduction of lactate (type A), underutilization of lactate (type B), or both (Madias, 1986). Metabolic acidosis is defined as an excessive accumulation of non-volatile acid manifested as a primary reduction in serum bicarbonate concentration in the body associated with low plasma pH. Certain conditions may exist with other acid-base disorders such as metabolic alkalosis and respiratory acidosis/alkalosis (Moe, Fuster, & Alpern, 2005). At the beginning of 21st century Robergs, Ghiasvand and Parker (2004) denied the former concept of lactate acidosis explanation of metabolic acidosis and advocated that it is not supported by fundamental biochemistry and has no research base of support. As concluded in their review, lactate production retards, not causes, acidosis. Moreover, they stated that research evidence shows that acidosis is caused by reactions other than lactate production. Every time ATP is broken down to ADP and Pi, a proton is released. When the ATP demand of muscle contraction is met by mitochondrial respiration, there is no proton accumulation in the cell, as protons are used by the mitochondria for oxidative phosphorylation and to maintain the proton gradient in the intermembranous space. It is only when the exercise intensity increases beyond steady state that there is a need for greater reliance on ATP regeneration from glycolysis and the phosphagen system. The ATP that is supplied from these nonmitochondrial sources and is eventually used to fuel muscle contraction increases proton release and causes the acidosis of intense exercise. Lactate production increases under these cellular conditions to prevent pyruvate accumulation and supply the NAD needed for phase 2 of glycolysis. Thus increased lactate production coincides with cellular acidosis and remains a good indirect marker for cell metabolic conditions that induce metabolic acidosis. If muscle did not produce lactate, acidosis and muscle fatigue would occur more quickly and exercise performance would be severely impaired (Robergs et al., 2004). Very soon Kemp (2005) and Kemp, Böning, Beneke and Maassen (2006) contradicted criticism of Robergs. Kemp (2005) considers the presentation, which ignores the pH dependence of the stoichiometry, does not show how the importance of this point decreases as pH of cells falls during exercise and that it does not in any case affect the logic of the traditional calculations, to be the main limitation of Robergs’ theory. Similarly, Lindinger, Kowalchuk and Heigenhauser (2005) point out that Robergs’s denial of the pH-dependence of stoichiometry has caused confusion.
Moreover, lactate acidosis is not only accompanied by high rates of ATP hydrolysis which is characterized for muscle contraction in the way of anaerobic glycolysis. Lactate is produced by most tissues in the human body during exercise, as well as at rest. The highest producers are muscle cells, brain and adipose tissue (Van Hall, 2010). In trauma patients acidemia is strongly correlated to serum lactate (Summersgill, Kanter, Fraser, 2015). As discussed later in this review, in case of hypoperfusion/hypoxemia or dysfunction of cellular metabolism (drug effects, malignancy, thiamine deficiency) significant lactate production occurs even without increased muscle work (Andersen, 2013). Numerous studies beginning with those of Pasteur in the 18th century demonstrated that anoxia and hypoxia stimulate cellular lactate acid production (Kelilin, 1966). In 1891, Araki (Karlsson, 1971) reported elevated lactate levels in the blood and urine of a variety of animals subjected to hypoxia. Nevertheless lactate production could be attenuated in the state of hyperoxia (Pupis, Slížik & Bartík, 2013; Suchý, Pupiš & Brunerová, 2014). It is still questionable to support Robergs’s concept which denies explanation of lactic acidosis causing metabolic acidosis.

EXERCISE PHYSIOLOGY OF LACTATE CLEARANCE

Despite of large mass, skeletal muscles are not unique producers or consumers of lactate. Other tissues such as brain, liver, kidney, heart, adipose tissue play an essential role in lactate production and clearance. At rest the contribution of lactate to oxidative energy production by heart is reported to be 10-15 % and could increase to 30 % during aerobic exercise (Gertz, Wisneski, Stanley, & Neese, 1988). Interestingly, the rate of carbohydrate oxidation by heart via lactate is higher than via exogenous glucose at rest and during exercise (Van Hall, 2010). Similarly lactate is an essential part of cerebral energy metabolism for astrocytes and neurons (Zielke, Zielke, Baab, & Tildon, 2007). The role of kidney in systemic lactate clearance is mainly in gluconeogenesis. Quantitatively, the importance of kidneys in lactate metabolism is comparable with liver. Liver is considered to be the most important tissue in net lactate clearance under resting conditions. The importance of lactate for the liver and kidneys seems as a carbon precursor for gluconeogenesis (Van Hall, 2010). Other tissue that contributes to lactate production and clearance is adipose tissue.

The rate of lactate release from adipose tissue may help diagnose disease profiles especially of type 2 diabetes (Merwe et al., 1998; Merwe et al., 2001). Lactate production in skeletal muscle has been studied for nearly two centuries and still its production and functional role at rest and during muscle contraction is a subject of debate. Historically, skeletal muscle was understood mainly as the site of lactate production during contraction and lactate production associated with a lack of muscle oxygenation and fatigue. Later, it was recognized that skeletal muscle not only plays an important role in lactate production but also in lactate clearance and this in turn has led to a renewed interest in the metabolic fate of lactate in skeletal muscle and also in other tissues (Van Hall, 2000). High-intensity exercise contributes to the production and accumulation of blood lactate in skeletal muscle and blood.

As resulted from the study of van Hall, Calbet, Sondergaard and Saltin (2002), the arterial lactate concentration can be maintained at a relatively low level despite a high lactate production during exercise with a large muscle mass because of the large capacity of active skeletal muscle to take up lactate. Lactate uptake is tightly correlated with lactate delivery. However, the limb lactate uptake during exercise is oxidized at rates far above resting oxygen consumption, implying that lactate uptake and subsequent oxidation are also dependent on an elevated metabolic rate. The elevated metabolic rate during active recovery after intense muscle work serves to promote lactate clearance via an accelerated rate of lactate oxidation (Brooks, 1991; Gladden, 2003). Therefore, active recovery after a strenuous exercise clears accumulated blood lactate faster than passive recovery. Muscle activity plays a key role in lactate metabolism. Although a number of attempts have been made to investigate the effects of other than active recovery modalities there was no benefit against passive rest. Manual massage has been studied for its potential effects on lactate clearance in long distance runners (Dawson, Dawson, & Thomas, 2011; Dawson, Kimberley, & Tidus, 2004), game players (Robertson, Watt, & Galloway, 2004) and boxers (Hemmings, Smith, & Graydon, 2000). It was generally confirmed that manual massage and passive recovery (Bielik, 2010) may have minimal differences on the physiological indices of muscle recovery. However, there is no commonly agreed intensity or mode of active recovery for clearing accumulated blood lactate. Menzies et al. (2010) studied clearance of accumulated blood lactate during recovery at
various exercise intensities. They proved that active recovery after strenuous exercise clears accumulated blood lactate faster than passive recovery but in an intensity-dependent manner. The ability to exchange and remove lactate was many times associated with physical fitness or trainability. Assumed that after exercise athletes with higher rate of blood lactate clearance have better regeneration and subsequent performance, Bret et al. (2003) compared whether running specialization (sprint runners vs. endurance runners) could be associated with differences in the ability to remove lactate. The overall ability to remove lactate did not differ significantly between the two groups. Similarly, Freund, Lonsdorfer, Oyono-Enguéllé, Lonsdorfer and Bogui (1985) did not find any differences in lactate exchange and removal abilities in untrained and trained healthy humans. However, in sedentary subjects, endurance training improves the lactate exchange and removal abilities estimated during recovery from exercises (Messonnier et al., 2001). Gharbi et al. (2008) advocate that the improvements in physical fitness are associated with a concomitant increase in the lactate removal ability. Contrary to that, Bielik (2014) did not find any significant correlation between the rate of lactate clearance and the performance restoration in elite cyclists. It is likely that the effect of physical training on lactate clearance after strenuous activity is characteristic for sedentary or lower fitness level athletes.

**PATHOPHYSIOLOGY OF LACTATE CLEARANCE**

Despite some controversy of lactate metabolism in exercise physiology, there is strong evidence that lactate metabolism is affected by disease states and health condition. There are many potential causes of lactate elevation in pathophysiology. In general, blood lactate elevation may be caused by production, decreased clearance ability, or a combination of both (Andersen et al., 2013). However, in pathophysiology elevated blood lactate is not undoubtedly and ordinarily defined. Most studies use cut-offs between 2.0 and 2.5 mmol/l (Kruse, Grunnet, & Barfod, 2011; Vandromme, Griffin, Weinberg, Rue, & Kerby, 2010; van Beest et al., 2013). Alike in healthy physically active men varies the rest blood lactate level generally between 1.5-2.5 mmol/l (Bielik, 2014; Janssen, 2001). The rest lactate levels in healthy subjects are influenced by such factors as hypoxic exposure, fasting and feeding. For instance, low glycogen stores in skeletal muscles and liver may decrease blood lactate levels at rest because lactate is considered as a precursor of lactate. lactate levels at rest because lactate is considered as a precursor of lactate. Almomen, Alsalem, Almomen and Badar (2011) found 50 % higher drop of lactate after exercise in the fasting group which elucidated by acceleration of lactate clearance from blood, probably by utilizing gluconeogenesis pathway.

In pathophysiology “high” lactate has been defined as a lactate level > 4mmol/l in a number of studies (Howell, Donnino, Clardy, Talmor, & Shapiro, 2007; Cox, Carney, Howell, & Donnino, 2008; Shapiro, Howell, & Talmor, 2005; Callaway, Shapiro, Donnino, Baker, & Rosen, 2009). Blood lactate level in exercise physiology and training after a strenuous exercise can reach >15 mmol/l (Bielik, 2010; Bielik & Papay, 2013; Janssen, 2001). Different approach in exercise physiology than the one discussed above is in very fast clearance of lactate in healthy subjects. The elevated blood lactate could be normalized within one hour even when passive resting would be applied. When light or moderate muscle work is performed, the clearance could be shortened by half of that time. In medicine and pathophysiology Andersen et al. (2013) divide elevated blood lactate into cases where it is driven by hypoperfusion/hypoxemia, and cases where it is not. The hypoperfusion and microcirculatory dysfunction includes the post cardiac arrest, regional ischemia, all forms of shock and trauma. In this case, blood lactate remains elevated and treatment is aimed to increase the tissue perfusion. Initial lactate levels and clearance are very often used for making morbidity and mortality prognoses. Septic shock is often associated with macrocirculatory dysfunction causing arterial hypotension, as well as microcirculatory dysfunction, and decreased oxygen and nutrient extraction by peripheral tissues (Andersen et al., 2013). In the study by Bolvardi et al. (2016) the lactate’s clearance in the dead group was significantly lower than the other group of patients with sepsis. Thus severe sepsis with lower lactate’s clearance is counted a high risk for mortality and organs’ dysfunction.

There is adequate support of literature establishing the clinical utility hyperlactatemia and lactate clearance as a prognostic indicator in adult cardiac surgical patients (Hajjar et al., 2013). Moreover, Ladha, Kapoor, Singh, Kiran and Chowdhury (2016) assessed the role of lactate clearance in determining the outcome in children undergoing
corrective surgery for tetralogy of Fallot. They found out that lactate clearance in the early postoperative period is associated with decreased mortality rate in children. Patients with higher lactate clearance have improved the outcome after 6 h compared with those with lower lactate clearance. Similarly Kalyanaraman et al. (2008) documented serial lactate levels to be beneficial for determining the outcome after cardiopulmonary bypass surgery in children. Especially they recognized “lactime”, time during which the lactate remains >2 mmol/l, to be the strongest predictor of mortality in their study. Badreldin et al. (2013) consider blood lactate as indispensable for mortality prediction after cardiac surgery and as concluded, its precision is higher than that of other commonly used “complex” scoring models.

In urgent medicine the rising body of literature demonstrates that blood lactate is a predictor of mortality following trauma, and that standard physiologic variables of systolic blood pressure and heart rate are not independent predictors of mortality in older trauma patients (Salottolo, Mains, Offner, Bourg, & Bar-Or, 2013). Determining initial blood lactate levels may improve the identification of circulatory hemodynamic instability, resuscitative efforts, and outcome of geriatric patients, particularly those with unrecognized hypoperfusion. However Gustafson et al. (2015) pointed some awareness of the predictive value of lactate. They found that the presence of ethanol in patients skews the relationship between lactate and base deficit. Thus resetting the threshold in which elevations in lactate and base deficit are associated with increased mortality. Peak lactate levels and the rate of lactate clearance may help identify a patient whose initially normal vital signs may mask an ongoing tissue hypoperfusion (Wo et al., 1993) and potentially serve as an endpoint to guide resuscitation (Odom, Howell, & Silva, 2013) or complete bundles of care used for resuscitation in trauma patients (Shafi et al., 2016).

Other cases not strictly associated to hypoperfusion with elevated blood lactate include malignancy (Yiu Chuen Choi, Collins, Gout, & Wang, 2013; Marchiq & Pouysségur, 2016), epileptic seizures (Yang et al., 2013), thiamine deficiency (Ramsi, Mowbray, Hartman, & Pageler, 2014; Campbell, 1984) or drug effects (Pham, Xu, & Moea, 2015). In these cases, the elevated lactate stems either from dysfunction of cellular metabolism or overproduction from increases in metabolism (Andersen et al., 2013).

Overall, the literature review from 33 selected articles supported blood lactate monitoring as being useful for risk assessment in patients admitted acutely to hospital, and especially the trend, achieved by serial lactate sampling, is valuable in predicting in-hospital mortality (Kruse et al., 2011). Hyperlactatemia is associated with in-hospital mortality in a heterogeneous intensive care unit population as based on total of 20,755 lactate analyzed measurements from 2,251 consecutive intensive care unit patients (van Beest et al., 2013).

CONCLUSION

Earlier image of lactate was generally seen as dead-end waste product of glycolysis resulting from muscle hypoxia, major cause of muscle fatigue or delayed onset muscle soreness. Today, lactate is considered a central player in cellular, regional and whole-body metabolism. Nevertheless, lactate production and clearance is encountered in clinical presentations and disease states. Patients with insufficient clearance or higher initial values may be at risk for morbidity or mortality.

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