Péronnet F

Lactate as an End-Product and Fuel

Laktat als Endprodukt und Brennstoff

Département de kinésiologie, Université de Montréal

SUMMARY

During high intensity short duration exercise, lactate (LA) accumulates at high concentrations ([LA]) because the contribution of anaerobic glycolysis to the ATP yield is large and LA clearance is much higher than LA production. Hydrolysis of glycolytic ATP releases H^+ which reduces muscle and arterial pH but in this type of exercise, higher [LA] is associated with better performances. For longer exercises at lower intensity the contribution of anaerobic metabolism to ATP yield is low but [LA] also increases and, for a given workload, is higher when O_2 availability and/or delivery is low and/or mitochondrial ATP production is impaired, and it has been suggested that LA accumulation during prolonged exercise reflects a deficit in aerobic ATP, and production of anaerobic ATP. An alternate explanation is that [LA] reflects the magnitude of homeostasis disturbances which translate into "error signals" for the stimulation of mitochondrial respiration: increase in redox potential and reduction in phosphate potential. This hypothesis is consistent with the observation that lower [LA] (hence smaller homeostasis disturbances) is associated with better endurance performances (although LA per se probably doesh not contribute to fatigue). LA produced in some working muscles during prolonged exercise, is released into the blood and taken up to be oxidized in other working muscles and/or other organs and tissues (lactate shuttle), thus sustaining aerobic metabolism. A portion can also be converted into glucose in the liver (Cori cycle) to sustain plasma glucose concentration. A great deal of attention has been paid to the relationship between [LA] and power output during ramp exercise, and a lot of effort and ingenuity have been invested to identify anaerobic and/or lactate thresholds which remain elusive and putative.

Key words: lactate, aerobic metabolism, anaerobic metabolism, lactate shuttle, lactate threshold.

ZUSAMMENFASSUNG

Bei hochintensiven Kurzzeitbelastungen ist der Anteil der anaeroben Glykolyse an der ATP-Gewinnung hoch und es wird mehr Laktat gebildet als eliminiert werden kann. Dementsprechend akkumuliert Laktat und die Konzentrationen steigt an. Bei der Hydrolyse des glykolytisch gewonnen ATPs wird H+ freigesetzt, das den muskulären und arteriellen pH-Wert senkt. Für diese Art von kurzzeitigen Belastungen sind höhere Laktatwerte mit größerer Leistungsfabgabe verbunden.
Bei längeren Belastungen niedrigerer Intensität ist der Beitrag des aneroben Metabolismus zur ATP-Gewinnung niedrig aber dennoch wird Laktat gebildet.
Bei einer bestimmten Belastungsintensität kann die Laktatkonzentration höher sein wenn die Sauerstoffverfügbarkeit oder –zufuhr niedrig oder und/oder die mitochondriale ATP Produktion beeinträchtigt sind. Es wird vermutet, dass die Laktat-Akkumulation bei Langzeitausdauerbelastungen ein Defizit in der aeroben und anaeroben ATP-Produktion reflektiert. Eine alternative Erklärung besteht darin, dass die Laktatkonzentration das Ausmaß der Störung der Homöostase widerspiegelt, welche wiederum zu Fehlermeldungen bei der Stimulation der mitochondrialen Atmungskette führt: Anstieg des Redox-Potentials und Rückgang des Phosphat-Potentials. Diese Hypothese stimmt mit der Beobachtung überein, dass geringere Laktatkonzentrationen, und damit Störungen geringeren Ausmaßes, mit einer höheren Ausdauerleistungsfähigkeit verbunden sind (auch wenn Laktat an sich nicht zur Ermüdung beiträgt). Laktat, das während Langzeitausdauerbelastungen in der Arbeitsmuskulatur gebildet wird, wird über das Blut in andere unbelastete Muskeln, Organe oder Gewebe transportiert und dort oxidiert (Laktat-Transport), wodurch der aerobe Metabolismus aufrecht erhalten werden kann. Ein gewisser Anteil an Laktat kann in der Leber zu Glukose abgebaut werden (Cori-Zyklus) um die Glukosekonzentration im Plasma zu erhalten. Großes Interesse gilt der Beziehung zwischen Laktat und der Leistung bei rampenförmiger Belastung sowie der Identifikation von anaeroben Schwellen und Laktatschwellen, die bislang schwer fassbar scheinen.

Schlüsselwörter: Laktat, aerober Metabolismus, anaerober Metabolismus, Laktat-shuttle, Laktatschwelle.

INTRODUCTION

The characteristics of lactate metabolism and the significance of plasma lactate concentration ([LA]) are different in response to short duration high intensity exercise and to prolonged endurance exercise, such as the 400-m race and the Marathon race taken as extreme examples (Figure 1 and 2).

HIGH INTENSITY SHORT DURATION EXERCISE

Anaerobic energy production

In response to short duration high intensity exercise the purpose of LA production is to provide a substantial portion of the energy yield: anaerobic glycolysis provides 47 kcal for each mole of glucose or glycosyl units fermented into 2 moles of LA [1]. Plasma as well as muscle [LA] concentration are easy to measure but the amount of lactate (LA) accumulated during exercise depends on the LA-space. The distribution of LA from working muscles to the blood, and from the blood to other tissues depends on intramuscular and blood pH, and on the density of LA transporters (MCT1, MCT4 and MCT2) [2] and on blood flow in working muscles and in other tissues. Accordingly, in a given situation the LA-space could vary and it is impossible to precisely estimate the amount of LA accumulated from muscle or plasma [LA]. Direct measures in animals [3] and indirect estimates in man [4,5] suggest that the average maximal amount of LA which

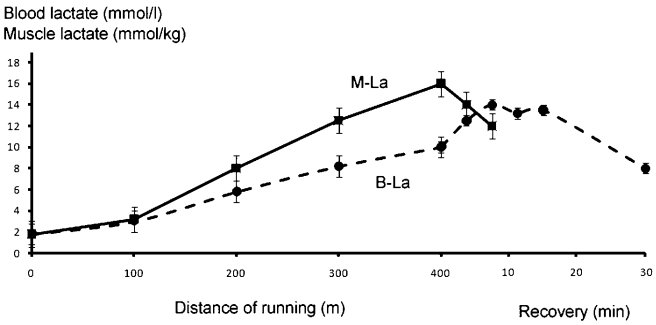

Figure 1: Plasma [LA] in response to a simulated 400-m. Redrawn from Hirvonen et al [34].

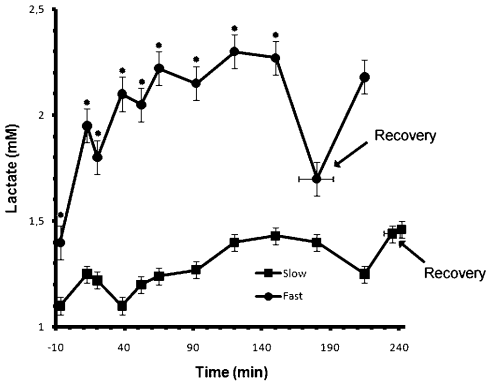

Figure 2: Plasma [LA] in response to a marathon race (slow: 3:45; fast: 2:45). Redrawn from O'Brien et al [17].

can be accumulated is ~1 g/kg or about ~800 mmoles in a 70-kg subject. This amount of LA which could be accumulated in ~30 sec correspond to the release of ~18.5 kcal (~78 kJ) in a 70-kg subject (maximal accumulation rate ~2.3 g/sec).

This represents, respectively, ~55, ~50, ~40 and ~25 % of the energy yield during 200, 400, 800 and 1500-m races [6] (~3500, ~1700, ~750 and ~350 W, respectively). Since plasma [LA] at the end of these races in actual competitions in elite athletes typically ranges between 20 and 25 mmol/L [7,8], assuming a total amount of LA accumulated of ~800 mmol (see above), the LA-space (800/20 or 25) ranges between 40 and 32 L (60-50 % body mass in a 70-kg subject).

LA production and efficiency of ATP synthesis

Based on these estimates of LA accumulation during short duration high intensity exercise it can be shown that in this situation anaerobic glycolysis is almost exclusively fuelled from muscle glycogen. Glycolysis could be fuelled either from plasma glucose which enters the muscle fiber trough facilitated diffusion and GLUT4 or from glucose-phosphate provided through glycogenolysis from muscle glycogen. The maximal rate of plasma glucose entry into peripheral tissues observed during hyperglycemic clamp during prolonged exercise does not exceed ~2 g/min [9]. Thus, a flux through glycolysis above ~2 g/sec can only be sustained from muscle glycogen. The large increase in muscle and plasma [LA] in response to short duration high intensity exercise is indeed associated with a sharp decline in glycogen concentration in working muscles [10].

There are two advantages of using muscle glycogen and not plasma glucose to fuel glycolysis during short duration high intensity exercise. The first advantage is to conserve plasma glucose, which is in short supply, to other organs, mainly the brain.

The second advantage is that, when compared to glycolysis from glucose (which requires 2 ATP to activate one mole of glucose), glycolysis from glycogen (which only requires 1 ATP and 1 Pi to activate one mole of glycosyl unit) provides more ATP (3 vs 2 moles of ATP/mole of glucose or glycosyl unit) [11] (p. 160). With 47 kcal released/mole of glucose or glycosyl unit, the efficiency of ATP resynthesis (~12 kcal/mole) by glycolysis is much higher from muscle glycogen (36/47 = 0.77) than from glucose (24/47 = 0.51) and is also higher than through aerobic metabolism (~0.6 for an average P/O of 3).

LA distribution and clearance

Based on estimates of LA accumulation during short duration high intensity exercise it can also be shown that the amount of LA accumulated is equal to the amount produced (i.e., there is essentially no LA clearance during short duration high intensity exercise).

The two major pathways of LA utilization during exercise are oxidation and conversion into glucose (gluconeogenesis, GNG) in the liver. However, both processes require ATP and thus oxygen: 0.750 L to oxidize 1 g of LA, and ~125-145 mL to convert 1 g of lactate into glucose or glycogen (6 and 7 ATP needed/mole glucose or glycosyl unit, respectively, with P/O = 3). During short duration high intensity exercise, the amount of oxygen consumed is low : e.g, < 2.5 L for a 400 m (computed from data reported by [12]).

Even under the assumption that all the oxygen available is used to oxidize LA, this is only enough oxygen to oxidize ~3.5 g of LA (vs ~70 g produced). As for the conversion of liver GNG, first, with an hepatic blood flow during exercise < 1.5 L/min [13], only a small portion of LA produced in the working muscle can reach the liver during the short period of high intensity exercise. Secondly, with a limited oxygen consumption in the liver (~70 mL/min) [13], which cannot possibly be entirely devoted to fuel GNG, the amount of LA which can be converted into glucose remains very low during a period of high intensity short duration exercise.

LA production/accumulation during short duration high intensity exercise

Finally, since anaerobic glycolysis with LA accumulation provides a substantial portion of the energy needed during short duration high intensity exercise, the highest the amount of LA produced and accumulated (these are the same) the better the performance. This has been shown, for example, in a study by Lacour et al. [8] conducted in elite 400-m runners. A close positive relationship was found between the average speed sustained and plasma [LA] at the end of the race (which, albeit imperfect, is a marker of LA accumulation) (Figure 3). Two other observations can be offered as evidence that performance in short duration high intensity exercise depends on the ability to produce and accumulate large amounts of LA. The very high running speeds sustained by greyhounds during 400- and 800-m races (~25 and ~60 seconds, respectively) are not only due to their very high VO_2max (~135 mL.kg-1.min-1) [14] but are also associated with very high post-race plasma [LA] (30-35 mmol/L) [15]. In contrast, patients with McArdle disease (type V

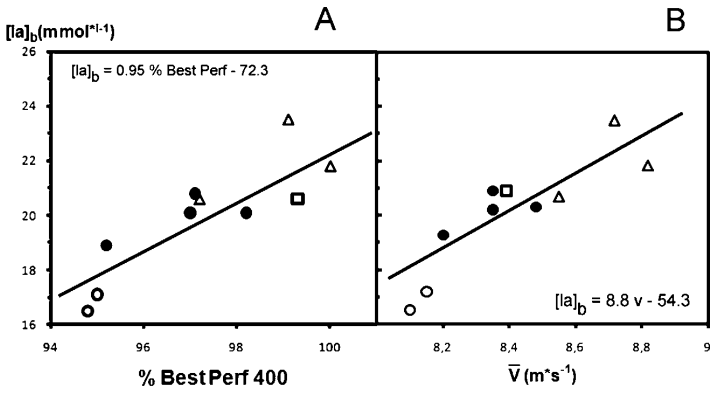

Figure 3: Relationship between performance for the 400-m (expressed as the average running speed [B] and the percentage of the best 400-m performance [A]) and plasma [LA] observed at the end of the race. Redrawn from Lacour et al [8].

glycogenosis due a deficiency of muscle phosphorylase) are unable to produce LA from muscle glycogen and are also unable to perform any type of short duration high intensity exercise [16].

PROLONGED ENDURANCE EXERCISE

Energy metabolism is entirely aerobic

In response to prolonged endurance exercise, plasma [LA] is much lower than in response to short duration high intensity exercise : depending on the fractional utilization of VO_2max sustained, training and nutritional states, and environmental conditions, the values range between 1.5 to 2 mmol/L [17] (i.e., only slightly above resting values) and ~10 mmol/L [18]. In addition, plasma [LA] are stable or slowly drift upwards (generally) or downwards (only at very low workloads). Under the assumption that the LA-space is stable, the slow changes in plasma LA over time, if any, suggest that the amount of LA present in the body remains fairly constant. As explained below, this does not indicate that LA is not produced, but that the rate of plasma LA disappearance closely matches its rate of appearance. Energy and ATP provided by glycolysis are only anaerobic when electrons which have been removed (along with hydrogen) when glucose or glycosyl units are oxidized in pyruvate, are accepted by pyruvate which is reduced into lactate which accumulates over time in the body. This is the case during short duration high intensity exercise (Figure 1).

However, when electrons and hydrogen which have been transiently accepted by pyruvate to produce LA are removed from LA to be finally accepted by oxygen to produce water, the energy and ATP provided by glycolysis are aerobic. The stability or near stability of plasma [LA] during prolonged endurance exercise (whatever the total amount of LA present and the level of plasma [LA]) indicates that the energy needed for this type of exercise is entirely provided by aerobic metabolism.

Indeed, indirect estimates of the percent contribution of anaerobic metabolism to the energy yield indicate that it is negligible for endurance exercise [5] except at the onset of exercise when plasma [LA] rises quickly (e.g., [18]), or during transient changes in pace for tactical reasons, such as the final sprint.

Table 1: Observations made in cyclists with a high and low endurance capability (mean ± SE; data from Coyle et al. [19]).

	High endurance capability n = 7	Low endurance capability n = 7
Age (years)	24.7 ± 1.4	24.1 ± 0.8
Body mass (kg)	71.1 ± 1.4	72.1 ± 1.5
VO_2max (mL.kg-1.min-1)	68.6 ± 1.2	66.6 ± 1.2
LT (%VO_2max)	81.5 ± 1.8	65.8 ± 1.7
%VO_2max	88.5 ± 0.5	88.0 ± 0.3
Time to fatigue (min)	60.8 ± 3.1	29.1 ± 5.0 (a)
Final plasma [LA]	7.4 ± 0.7	14.7 ± 1.0 (a)

(a): significantly different than in subjects with a high endurance capability ($P < 0.05$)

Plasma [LA] and endurance performance

The higher the plasma [LA], the better the performance during short duration high intensity exercise (see above). In contrast, for a given fractional utilization of VO_2max, exercise time to exhaustion is longer (i.e., endurance capability is higher) in subjects with the lower plasma [LA]. This is well exemplified in the study by Coyle et al. [19] summarized in table 1: the subjects with lower plasma [LA] during a simulated bike race at 88%VO_2max were able to sustained this workload almost twice longer than those with the highest plasma [LA]. When compared to the subjects with the lowest endurance capability, the LA curve (i.e., plasma [LA] plotted against %VO_2max) during incremental exercise to VO_2max, was shifted to the right in subjects with the highest endurance capability. The « LA threshold » (LT) defined in this particular study as the %VO2max when plasma [LA] was 1 mmol/L above the basal value, was observed at 65.8%VO_2max in subjects with the lowest endurance capability vs 81.5%VO_2max in subjects with the highest endurance capability.

LT and endurance performance

Based on this observation, which has been repeatedly confirmed, it is generally accepted that the LT identified during incremental exercise or during prolonged exercises at constant workload (maximal lactate steady state or MLSS), is a valid index of endurance capability [20]. Although this observation is interesting and can have practical applications, it should be recognized that the term LT is a misnomer since there is obviously no threshold in the LA curve. This is precisely the reason why more than twenty different LTs have been suggested all of them based on purely geometric analysis of the LA curve without any physiological justification and significance. In addition, in almost all the studies showing good correlations between performance and a particular LT, the LT was expressed in running speed, VO_2 or power output (i.e., absolute LT).

However, the absolute LT depends in a large extent on VO_2max, which is itself a major determinant of performance for events lasting longer than about 60 seconds [21]. Thus, in any relationship between absolute LTs and performance, VO_2max is a confounding factor which has seldom been controlled. This is

probably why the absolute LTs are not selective determinants of performance in endurance events but also of performance for shorter distances such as the 800-m running and the 4-km cycling [20].

The LA shuttle

During prolonged endurance exercise, although plasma [LA] is stable or almost stable, measurements of plasma LA kinetics show that LA is continuously produced in some tissues and utilized in others, but that the rate of plasma LA appearance and disappearance are similar or very close. The flux of plasma LA from the sites of production to the sites of disposal has been described as the cell-to-cell LA shuttle [22-25]. Studies of LA release and uptake across various vascular beds using selective catheterisation techniques, coupled or not with tracer techniques, have shown that the sources of plasma LA during prolonged exercise are the working muscles but also the non-working muscles, and that these tissues along with the heart, the brain and the liver are also the sites of plasma LA removal. In the liver, LA can be converted into glucose which can be released into the blood to sustained glycaemia in a situation where plasma glucose utilization is increased. Thus, the LA shuttle, coupled with liver GNG, is a way to maintain plasma glucose concentration at the expense of muscle glycogen (it should be remembered that glucose cannot be directly released into the blood from muscle glycogen, due to the absence of glucose 6-phosphatase).

In the heart and brain, the LA removed from the blood is oxidized and the LA shuttle, thus, could be seen as the way to fuel aerobic metabolism in these organs also at the expense of the large stores of muscle glycogen, thus sparing plasma glucose and the much smaller liver glycogen stores. Finally, the LA shuttle from non-working to working muscles can also be seen as way to sustain aerobic metabolism in working muscles at the expense of glycogen stores in non-working muscles, glycogenolysis in non-working muscles being probably stimulated by the increase in plasma epinephrine concentration [24]. The significance of the shuttle of LA from working muscles, where it is produced, back to the same working muscles, where it is oxidized, is less obvious: the same result could be obtained with the lactate directly oxidized in the muscle fibers where it is produced, or in adjacent fibers, i.e, through an intramuscular shuttle [26-28]. There are two reasons for the shuttle of LA from the working muscles back to the working muscles through the circulation. The second reason is described in the following section which explains why muscle and plasma LA concentrations during prolonged exercise are higher than at rest, although the entire organism is aerobic. The first reason is that this shuttle allows the LA which is probably mainly produced in glycolytic fibers to be taken up by oxidative fibers.

SIGNIFICANCE OF PLASMA [LA] DURING PROLONGED EXERCISE

Anaerobic threshold ?

During prolonged exercise the energy is entirely produced through aerobic metabolism. However, plasma [LA], which is stable or almost stable is higher than at rest and can reach values as high as 10 mmol/L [18]. Furthermore, for a given workload, plasma [LA] is stable but at a higher value in all situations where the availability of oxygen (normobaric or hypobaric hyoxia), oxygen transport (impairement in alveolar ventilation, in oxygen diffusion, in oxygen carrying capacity of the blood, in cardiac output, etc.), and oxygen utilization (mitochondrial disease, detraining) are impaired, and conversely [29]. Under the well entrenched theory of the anaerobic threshold, these observations are offered as the best experimental support showing that above a certain workload and VO_2, anaerobic metabolism (with LA accumulation) has to be involved in ATP generation because aerobic energy supply becomes insufficient. This theory and explanation, however, cannot account for the facts 1) that there is actually no anaerobic energy provided when plasma [LA] is stable, whatever plasma [LA] (a good example is rest, a situation where nobody will seriously claim that a portion of the energy derives from anaerobic metabolism, but where plasma [LA] is about 1 mmol/L but stable); and 2) that a decrease in oxygen availability, or impairment in oxygen transport and utilization (although they can reduce VO_2max) do not modify VO_2 for a given submaximal workload.

Marker of the error signals for mitochondrial respiration

The best (and simpler) explanation for the fact that plasma [LA] is stable or almost stable but higher than at rest during prolonged exercise is that it is a marker of error signals needed to stimulate mitochondrial respiration and production of aerobic energy and ATP [24,30]. The two factors which stimulate mitochondrial respiration are an increase in redox potential and a decrease in phosphate potential [31,32]. In situations where aerobic ATP production is compromised (decrease in oxygen availability, or impairment in oxygen transport and utilization) but where there is room for compensation, mitochondrial VO_2 and aerobic ATP production are maintained at the cost of a lower phosphate potential and a higher redox potential (the latter being due for a large part to the reduction in phosphate potential). In other words, the cost to pay for a similar VO_2 and aerobic energy production is a larger disturbance in cell homeostasis and larger error signals which control mitochondrial respiration. In the cytosol, the lower phosphate potential stimulates glycolysis, increasing redox potential (NDH_2/NAD) and, as consequence, the LA/pyruvate ratio, and muscle and plasma [LA].

The significance of plasma [LA] as a marker of the error signal which stimulate mitochondrial VO_2 explains that reliable hallmarks of a high endurance ability are a lower plasma [LA] at any submaximal level of exercise and VO_2, a right shift of the LA curve and a higher LT (which does not exist [33] but is a marker of the position of the LA curve, whatever the particular criterion chosen for "LT").

Competing interests: none

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Correspondence:
François Péronnet
Emeritus professor
Département de kinésiologie, Université de Montréal
CP 6128 Centre-Ville, Montréal, QC, Canada H3C 3J7
Phone: 1 514 743 6737
Fax: 1 514 343 2181
E-Mail: francois.peronnet@umontreal.ca