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# THE LIMITS OF PERFORMANCE AT HIGH ALTITUDE

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## ABSTRACT

The intensity of maximum exercise involving a large muscle mass that an acclimatized lowlander can sustain at altitude is reduced compared to sea level. In fact, exercise is stopped before the appearance of biochemical signs of peripheral fatigue. One possible hypothesis to explain the reduction of classical biochemical signs of fatigue in the muscle after exhaustive exercise at high altitude could be that central fatigue, induced by a maximally stressed respiratory system, would possibly limit such exercise with large muscle groups before their full potential is elicited. It appears that in controlled laboratory conditions at 5050m the muscular apparatus by itself remains in good condition and in principle capable for work .This seems to be the case only when a small muscle mass is activated. Exhaustion time of dynamic fore arm work at the identical absolute (maximum) load is the same at sea level and altitude, and similar signs of peripheral muscle fatigue develop before exhaustion is reached. By contrast, for similar exhaustion time, the absolute maximum cycling load maintained at 5050m is ~20% lower than at sea level. Furthermore, while exhaustion during leg exercise at sea level is accompanied both by biochemical and electromyographical signs of peripheral fatigue, this is not the case at high altitude. Thus, at altitude, central rather than peripheral fatigue limits exhaustive exercise carried out with large muscle groups. Such mechanism could , at least partially, explain the decreased accumulation of lactic acid in blood in acclimatized subjects during exhaustive exercise at high altitude ("'lactate paradox' ) and may represent a possible strategy for preserving vital respiratory functions from failure at altitude. Indeed at high altitude, the diaphragmatic contribution to ventilation during exercise at the same relative load decreases with time. This seems to be due to diaphragmatic fatigue, which hypothetically may contribute to exercise limitation at high altitude, although other mechanisms, like decreasing oxygen availability at the level of the central nervous system, may also play a role in limiting the duration of exhaustive exercise in conditions of chronic hypobaric hypoxia. **(Acta Andina 1996, 5:23-30)**

Keywords: exercise, lactic acid, muscle, fatigue, altitude, diaphragm

## RESUMEN

La intensidad del ejercicio máximo, comprometiendo una masa muscular grande, que un sujeto puede sostener en la altura está reducida. En realidad, el ejercicio se interrumpe antes que aparezcan los signos bioquímicos de fatiga periférica. Una posible hipótesis para explicar la reducción de los clásicos signos bioquímicos de fatiga en el músculo despúes del ejercicio exhaustivo en la altura podría ser que la fatiga central, inducida por un sistema respiratorio máximamente estresado, podría posiblemente limitar tal ejercicio con largos grupos musculares, antes que se evidencie su pleno potencial . Parece ser que bajo condiciones de laboratorio controladas a 5050m el aparato muscular en sí, permanece en buenas condiciones y en principio apto para trabajar. Este parece ser el caso solo cuando una pequeña masa muscular es activada. El tiempo de agotamiento de trabajo dinámico del antebrazo a idéntica carga absoluta (máxima) es el mismo a nivel del mar que en la altura, y los signos de fatiga muscular periférica se presentan antes que se llegue al agotamiento. En contraste, para tiempos similares de agotamiento, la carga máxima absoluta en la bicicleta ergométrica mantenida a 5050m es ~20% mas baja que a nivel del mar. Más aún, mientras el agotamiento durante el ejercicio de piernas a nivel del mar es acompañado por signos bioquímicos y electromiográficos de fatiga periférica, este no es el caso en la Altura. Por lo tanto, en la altura, el agotamiento central en vez de periférico limita el ejercicio exhaustivo llevado a cabo en grandes grupos musculares. Tal mecanismo podría, por lo menos parcialmente, explicar la disminuída acumulación de ácido láctico en la sangre de los sujetos aclimatizados durante el ejercicio exhaustivo en la altura (lactate paradox') y puede representar la posible estrategia para evitar la falla de las funciones respiratorias vitales en la altura. En la altura la contribución diafragmática a la ventilación durante el ejercicio a la misma carga relativa disminuye con el tiempo. Esto parece ser debido a fatiga diafragmática, que hipotéticamente puede contribuir a la limitación del ejercicio en la altura, a pesar de que otros mecanismos, como el disminuir la disponibilidad de oxígeno a nivel nervioso central, puede jugar un rol en limitar la duración del ejercicio exhaustivo en condiciones de hipoxia hipobarica crónica. **(Acta Andina 1996, 5:23-30)**

Palabras claves: ejercicio,ácido láctico, músculo, fatiga, altura, diafrágma.

The aim of this article is to briefly discuss the so-called "lactate paradox", i.e. the drastic reduction of the maximum accumulation of lactate in blood ( [La] max ) during intense exercise observed in acclimatized lowlanders at altitude when compared to sea level.

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## Lactate at altitude : the early observations

The first observations on blood lactate ([La]) during exercise at altitude were made by Dill et al. (1931). At altitude at a given work load [La] initially rose higher than at sea level, but after acclimatization reached sea level values again. In subjects acutely exposed to altitude Edwards (1936) also reported higher [La] levels at sub-maximum power outputs but similar [La]max. After acclimatization [La] levels at sub-maximum power outputs had returned close to sea level values whereas [La]max had decreased. Edwards thought that the decrease in [La]max during acclimatization to altitude might be explained by the reduced alkali reserve, by an altered enzyme activity or by diaphragmatic fatigue (Edwards, 1936). Cerretelli (1967) showed

that the decreased alkali reserve at altitude indeed shifts the slope of the line relating [H+] to [La] in blood after exercise and he argued that a lower intracellular pH for a given [La] could possibly impair the activity of glycolytic enzymes like phospho-fructo-kinase.

### The paradox

In 1986 West measured a $PaCO_2$ on Everest of 7.5 Torr and calculated a resting $PaO_2$ of 28 Torr implying an even lower value during exercise. Despite this extreme hypoxemia no [La] accumulation would take place when extrapolating West's graph (adapted from Cerretelli, 1980) (Figure 1): *'If this extrapolation held good, a well acclimatized climber who reached the summit of Mount Everest without suplementary oxygen would have no blood lactate. This is a paradox indeed, because such a climber is apparently more hypoxic during maximal exercise than in any other known situation'* (West, 1986). In contrast with this prediction, during Operation Everest II (OE-II, a simulated climb of Mt. Everest) it was observed that exhausting exercise at a pressure equivalent to the summit of Mt. Everest resulted in a small but significant increase in blood [La] (Sutton et al., 1988; Young et al., 1992).

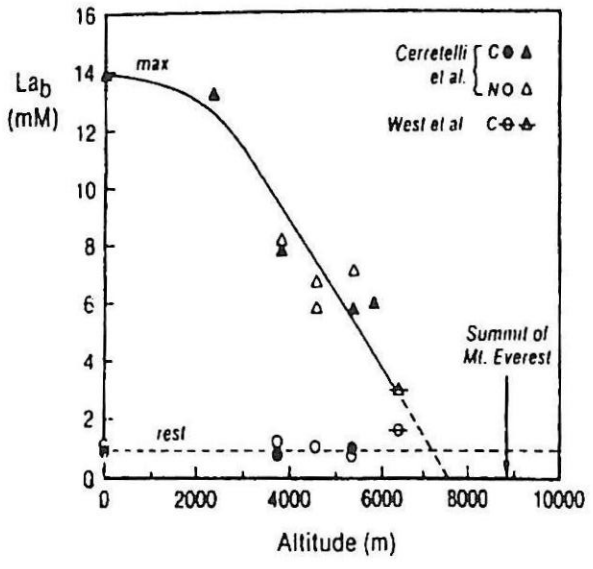


Figure 1:Maximal blood lactate (Lab) as a function of altitude. Most of the data are redrawn from Cerretelli et al (1982). The filled circles and triangles show data for acclimatized Caucasians (C); the open circle and triangles are for high-altitude natives (N). The data for 6300m are from acclimatized lowlanders. Extrapolation of the lineline to the horizontal axis suggests that a climber who reaches the summit of Mount Everest without supplementary oxygen will have no blood lactate (from West,1996).

The term *"lactate paradox"* was introduced by Hochachka(1989). He defined it as *"during incremental aerobic exercise test to fatigue* under hypoxic conditions they **(the Quechuas, South-American high altitude natives)** ***form less lactate and accumulate it to lower levels than normoxic lowlanders'*** **(Hochachka, 1989)**. After 6 weeks of deacclimatization at sea level these subjects were still unable to accumulate as much [La] as lowlanders during fatiguing cycling exercise and he concluded that it was therefore the expression of a fixed metabolic feature (*'the perpetual lactate paradox'*). Recently in a review by Reeves et al. (1992) of data obtained on lowlanders during OE-II and in work carried out on Pike's Peak, the lactate paradox was defined at the situation *'in which blood lactate accumulation during exercise is increased on arrival at high altitude but falls with acclimatization'*

### Recent observations

The buffer capacity hypothesis was tested at 5050m during exercise at V $O_2$ max, with or without prior oral sodium-bicarbonate ingestion (Kayser et al., 1993b). Despite normalized buffer stores after bicarbonate ingestion at altitude [La]max levels did not increase and exercise was interrumpted with both muscle and blood pH higher than at sea level. The hypothesis was therefore rejected.

The muscle resting glycogen level seems unaffected by chronic hypoxia (Green et al., , 1989; Young et al., 1982). Upon arrival at altitude a standardized exercise causes a glycogen depletion greater than at sea level. After acclimatization the depletion is the same again as at sea level (Green et al., 1992). This muscle glycogen sparing effect upon acclimatization was atributed to a lesser B-adrenergic stimulation of glycogenolysis (Brooks et al. 1991c) and to a lesser dependance on intra-muscular glucose sources (Green et al., 1992; Brooks et al., 1992). In any case, a lack of muscle glycogen stores does not seem to be at the basis of the "lactate paradox".

The activity of several glycolytic enzymes in the vastus lateralis of climbers after a 6-8 week exposure to 5000-8600m was unchanged compared to pre-exposure (Howald et al. 1990)

which confirmed earlier results, including data on total glycogen phosphorylase (Green et al. 1989; Young et al. 1984). A slight decrease in phospho-fructo-kinase (PFK) activity at 4300m was found, but that was explained as a consequence of a changed glycolytic control rather than a cause (Green et al. 1992). By and large, it seems that the main regulatory enzymes of the glycolytic pathway are not affected by chronic pypoxia.

But, since enzyme activity is measured on homogenized muscle tissue in vitro it can only partially describe regulatory metabolic mechanisms in vivo and the hypothesis that a modulation of enzymatic metabolic control of glycogenolysis or glycolysis may be at the basis of the "lactate paradox" can not be ruled out. Indeed, even if total muscle glycogen phosphorylase is not altered at altitude (Green et al., 1992;Young et al., 1984) it remain possible that an increased activation of phosphorylase "b" to its active form a, for example during the initial phase at altitude when adrenaline levels are high, may lead to increased glycogenolysis.

After 18 days acclimatization at 4300m a decrease in the net lactate release from the exercising legs was observed (Bender et al. 1989). This decrease could be to a reduced production or to an increased removal of lactate. Recently the net rates of appearance and disappearance of lactate and glucose at rest and during exercise at sea level and at 4300m were determined (Brooks et al., 1991b; Brooks et al.;1991c; Brooks et al.,1992; Green et al.,1992; Mazzeo et al.,1994). Infusing isotope labeled lactate and glucose and sampling effluent blood from the limbs these authors were able, among others, to measure the net release and uptake of lactate and glucose by the limbs. Acute exposure to hypoxia would increase adrenaline release, which would stimulate glycogenolysis and glycolysis, leading to increased lactate release (Brooks et al.,1992). With acclimatization adrenergic drive would subside and the stimulation of glycolysis would decrease. Indeed, B-blockade decreased the amplitude of the effect of acute altitude exposure on glycolysis, and blood [La] during exercise was lower than in the control condition, although still higher than at sea level. However, it did not prevent the progressive decrease in exercise blood [La] that accompanies acclimatization to high altitude, although the amplitude of the decrease was considerably less (Mazzeo et al.,1994). Thus, the "lactate paradox" cannot be fully explained by an alteration of adrenergic control of glycolysis alone (Mazzeo et al., 1994).

During OE-II at low barometric pressures bicycle exercise induced exhaustion with less biochemical signs of muscle fatigue than at sea level (Green et al., 1989). On the other hand, since nerve conduction velocity, muscle end-plate transmission and muscle excitation-contraction coupling appear not to be altered by prolonged altitude exposure, the function of the neuromuscular system does not seem to be affected (Garner et al.,1991; Kayser et al., 1993a, Kayser et al., 1993d). Bigland-Ritchie and Vollestad (1988) hypothesized that at high altitude central (neural) rather that peripheral (metabolic) fatigue limits dynamic exhaustive exercise with large locomotor muscle groups. A maximally stressed respiratory system would, via the central nervous system, limit the central drive to large muscle groups before their full potential is reached. Indeed, acclimatized subjects at 5050m could sustain exercise with a small muscle group at the same absolute load, for the same time and with similar signs of peripheral fatigue as at sea level, whereas exhaustion of maximum whole body exercise, although performed at a lower absolute load, was reached after similar time but with no signs of peripheral fatigue (Kayser et al. 1994). At altitude the diaphragm fatigues during cycle exercise at 75% of V $O_2$ max (Cibella et al., 1992;Kayser et al., 1993b) and could provide an input to the central nervous system leading to a decrease in central drive to the active locomotor muscles. A recent experiment performed at 5200m does not seem to support this hypothesis.

Acclimatized subjects performed repeated maximal isometric voluntary contractions before and during exhausting bicycle exercise with or without 4% inspiratory $CO_2$. With added $CO_2$ ventilation was higher, whereas the maximum voluntary contraction force of the forearm flexors at exhaustion was unchanged. The authors concluded that no decrease in central drive to the respiratory muscles or locomotor muscles had ocurred (Savard and Saltin, 1991). Thus, the origin of the signals leading to the cessation of the central drive at exhaustion from leg exercise at altitude remains unclear. The respiratory and/or other higher nervous centers, with or without contribution of the fatigued respiratory muscles and/or of decreased arterial $O_2$ saturation, are possible candidates. Nevertheless, the proposed mechanism of central limitation is compatible with the absence of signs of peripheral fatigue at the end of

exhausting maximum exercise with large muscle groups at altitude and with the lower levels of [La]max.

### A working hypothesis: Acute hypoxia

Lowlanders exposed to acute hypoxia react to this stressful event with increased circulating adrenaline levels (Young et al., 1989; Young et al., 1991; Mazzeo et al., 1991; Mazzeo et al., 1994). This would stimulate, through muscle ß-receptors, the transformation of phosphorylase "b" to its active form "a", thus increasing the rate of splitting of glycogen to glucose monomers.

Since for a given level of sub-maximal power output oxidative phosphorylation (i.e. $VO_2$) would remain constant, through a mass-action effect, disproportionate high levels of pyruvate would result in a spill-over into lactate formation leading to higher muscle and blood [La] (Brooks et al., 1991c; Green et al., 1989; Green et al., 1992). During prolonged sub-maximal exercise a new steady state would be attained with stable but higher [La] levels than in normoxia but the same $V O_2$ (Brooks et al., 1992). Since maximum power output is decreased, the maximum rate of oxidative phosphorylation (i.e $V O_{2max}$) is also diminished and $[La]_{max}$ is similar to that at sea level, whereas for any given absolute sub-maximum work rates, [La] is higher. As a result, glycolysis appears to be slightly uncoupled from oxidative phosphorylation (Green et al., 1992). (also see figure 2).

### Chronic hypoxia

At altitude the maximum power output that can be sustained during whole-body exercise reduced, possibly by a mechanism of central fatigue. Since the energy cost of muscular contraction *per se* is not altered by hypoxia, the maximal rate of TCA cycling is decreased in proportion. Thus, glycolytic flow into the TCA cycle is also decreased, simply by mass-action effect; and, if the coupling of glycolysis to oxidative phosphorylation would remain constant, [La] accumulation would depend only on exercise intensity and duration, and on the blood lactate removal.

It is conceivable that, in analogy to what happens on lymphocytes for ß2-receptors as well as in the heart for ß1-receptors (Richalet et al., 1990), chronic hypoxia may induce a down

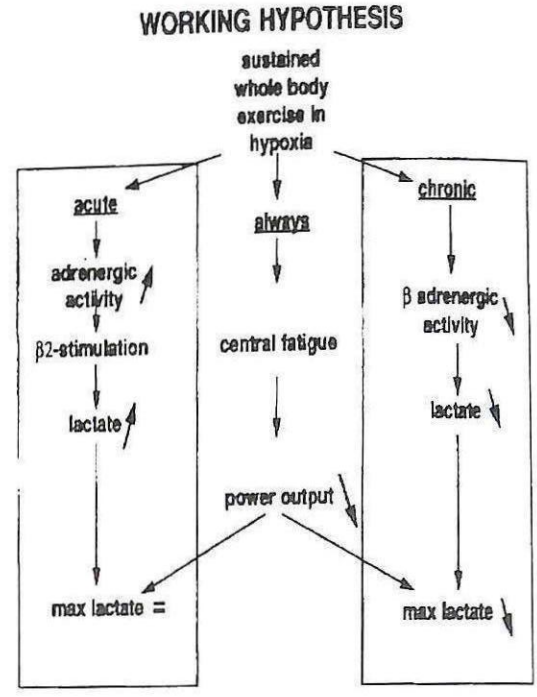


Figure 2.-A diagramatic representation of a hupothetical explanation of the "lactate paradox" in lowlanders going to high altitude. The middle panel shows that maximum vhole-body exercise capacity is decreased through a mechanism of central limitation of the sustainable maximum power output of dynamic exercise. The left panel explains why through the increased adrenergic drive in acute hypoxia increased glycolysis may still lead to high maximum lactate levels, be it is shown how in the acclimatized state a cedreased glycolytic activity in chronic huposia, coupled to the decreased maximum power output, would lead to near normal sub-maximal, but lower maximum blood lactate levels, the latter being the "lactate paradox".

regulation of ß-receptors also in skeletal muscle, thereby diminishing the glycogenolytic effect of adrenaline. Whatever the mechanism, in the course of acclimatization, [La] values attained at sub-maximal exercise intensities decrease as compared to acute hypoxia. Since the maximum power output that can be sustained and consequently the maximal rate of oxidative phosphorylation ($VO_{2max}$) are decreased, $[La]_{max}$ would also decrease and the "lactate paradox" would be established. As a result, glycolysis would appear to be more tightly coupled to oxidative phosphorylation in chronic hypoxia than in acute hypoxia.

Since, in acclimatized subjects exercising in acute normoxia, the maximum power output and the maximum oxygen uptake are increased as compared to hypoxia, one also would expect $[La]_{max}$ to increase. Grassi *et al.*(pers.comm.) recently observed that $[La]_{max}$ of acclimatized lowlanders at 5050m does not attain sea level values while breathing an oxygen enriched gas mixture, confirming previous observations (Cerretelli,

1980; Edwards, 1936). These results suggest that the "lactate paradox" is not only dependent on the rate of oxidative phosphorylation and that other unknown regulatory mechanisms of metabolism also play a role.

### Lactate accumulation in altitude natives

Also Sherpas, high altitude natives of Tibetan origin living in the Nepalese Himalaya, as well as high altitude South-American Indians are characterized by low $[La]_{max}$ values (about 6 mM) [Cerretelli, 1980; Cerretelli et al. 1982; Cerretelli and diPrampero, 1985]. Most research corcerning adaptation to high altitude in altitude native populations has been conducted by taking scientific equipment into the field and by studying the experimental subjects in their habitat. Few observations were performed on natives brought down to sea level (Cerretelli, 1980; Cerretelli et al. 1982; Cerretelli and diPrampero, 1985; Hurtado, 1932; Paz Zamora et al., 1982). Hochachka and colleagues changed the research strategy by taking six Quechua Indians, born and living essentially all of their lives at altitudes ranging from 3600 to 4500m, to sea level (Hochachka, 1989; Hochachka et al., 1991; Matheson et al., 1991). Among other results they reported that the Andean natives also display the "lactate paradox" (Hochachka, 1989). In lowlanders acclimatizing to high altitude the onset of the "lactate paradox" has a half time of about ~5 days (Grassi et al., 1992). Upon return to sea level normal $[La]_{max}$ values are attained after a few weeks, also with a half time of ~5 days (Grassi et al., 1992). By contrast, even after 6 weeks of deacclimatization the Quechuas were still unable to accumulate as much [La] as lowlanders during exhausting bicycle exercise (Hochachka et al., 1991). Based on results obtained by $^{31}$P-NMR spectroscopy they tentatively explained their findings by a tighter coupling of glycolysis to oxidative phosphorylation in the working muscle of the Quechuas. Skeletal muscle of these subjects would possess characteristics similar to those found in heart muscle (Katz et al., 1989). Such a shift towards the "cardiac spectrum" would be presumably mediated through a different enzymatic control of aerobic glycolysis (Hochachka, 1992).

Tibetans born at low altitude (1300m, Kathmandu, Nepal) from parents that came originally from the Tibetan plateau (3500-5000m) have the same maximum aerobic power, $[La]_{max}$ mechanical efficiency during cycling and t½ $VO_2$-on at ~50% of $VO_{2\,max}$ when compared to a local lowland control group, indicating that the metabolic response to an exercise stress, in particular lactate accumulation in blood, are similar in the investigated groups (Kayser et al., 1994). Thus, the "lactate paradox" is not present in subjects that genetically are highlanders but that are born and living at low altitude. The presence of the "lactate paradox" in highlanders born and living at high altitude must therefore be an acquired characteristic as it is for acclimatized Caucasians. The fact that in the Quechuas it does not disappear within six weeks of sojourning at sea level is intriguing, but does not nesessarily imply that it is a permanent feature. It cannot be excluded that deacclimatization over a longer period than 6 weeks would, also in Quechuas, increased [La] max.

### Conclusions

Since, at altitude, at any given whole-body exercise intensity, mass oxygen transport to the contracting locomotor muscles is not altered by the process of acclimatization, the gradual reduction in [La] max in lowlanders exposed to chronic hypoxia (i.e. the "lactate paradox") is not due to changes in oxygen availability at the tissue level. At present it appears that the "lactate paradox" is the result of a least two mechanisms: a) a decrease in maximum substrate flux through oxidative phosphorylation due to central limitation of sustained maximum power output in hypoxia, and b) alterations in the metabolic control of glycogenolysis and glycolysis at the cellular level. With regard to the differences in lactic anaerobic metabolism observed between lowlanders and highlanders, both groups being acclimatized or not, these do not seem merely to reflect points along the same continuum of phenotypic adaptation of which the location depends on the time spent at altitude. In any case, the exact mechanisms at the base of the "lactate paradox", both in lowlanders and highlanders, are still matter for further investigation.

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