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Why is endurance performance decreased at high altitude?

Abstract

Endurance performance at high altitude is decreased as compared to low altitude whereas explosive power and sprint performance are maintained. Despite considerable research the mechanisms behind this impairment in endurance, even though obviously causally related to the decreased partial pressure of oxygen in the ambient air, are not fully understood. Endurance exercise with large muscle groups at altitude is ended at exhaustion with less limb locomotor muscle fatigue and with sub-maximal cardiac output. It is hypothesized that the central nervous system limits motor drive. Motor unit recruitment sets metabolic rate and hence oxygen transport, even though at very high altitude several steps in the oxygen transport cascade clearly become limited in their capacity. The extra oxygen cost of extreme hyperventilation is off-setting the resulting gain in oxygen uptake; increases in cardiac output are off-set by decreased alveolar capillary transit times leading to less oxygen saturation of haemoglobin; and peripheral oxygen extraction may reach high near maximal values. Limitation of endurance performance in acute or chronic hypoxia is multifactor, even though limitation is necessarily set by the extent and duration of recruitment of muscle by the central nervous system. The mechanisms setting the maximal sustainable levels of recruitment remain to be elucidated.

Résumé

La performance en endurance est diminuée en haute altitude par rapport à basse altitude tandis que la puissance explosive et la performance en sprint sont maintenues. En dépit d'une recherche considérable les mécanismes de cette diminution en endurance, quoique évidemment dus à la diminution de la pression partielle de l'oxygène dans l'air ambiant, ne sont pas entièrement compris. L'exercice en endurance en altitude avec des grands groupes musculaires est arrêté, à l'épuisement, avec moins de fatigue musculaire et avec un débit cardiaque sous-maximal. L'hypothèse est avancée que l'activation motrice est limitée par le système nerveux central. Le recrutement d'unités motrices détermine le taux métabolique et ainsi le besoin en transport en oxygène, même si en altitude très élevée plusieurs étapes dans la cascade du transport d'oxygène deviennent clairement limitées dans leur capacité. Le coût supplémentaire en oxygène de l'hyperventilation extrême annule le gain dans la prise d'oxygène; toute hausse du débit cardiaque est compensée par des temps de passage dans les capillaires alvéolaires diminués induisant une moindre saturation de l'hémoglobine avec l'oxygène; et l'extraction périphérique de l'oxygène atteint des valeurs élevées proches du maximal. La limitation de l'endurance dans l'hypoxie aiguë ou chronique est multifactorielle, quoique ce soit nécessairement le système nerveux central qui limite l'ampleur et la durée du recrutement des muscles. Les mécanismes qui limitent ces taux maximaux soutenables du recrutement restent à élucider.

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Introduction

Reinhold Messner, a world famous mountain climber, and the first person to have climbed all fourteen 8000 meter summits in the Himalaya, writing about his experiences a few meters from the top of Mt. Everest during his solo ascent without supplementary oxygen in 1980 said: *«Once more I must pull myself together. I can scarcely go on… I consist only of will. After each few metres* (climbing up*) this too fizzles out in an unending tiredness.»* (Messner, 1981) Before proving that climbing Everest, just breathing the shallow ambient air, was actually possible (during the very first «oxygenless» ascent of Messner with his fellow climber Peter Habeler in 1978), scientists had debated whether it would at all be possible to reach the summit without the use of bottled oxygen. Many had actually doubted it because of the extremely low partial pressure of oxygen in the air on the summit (~53 mmHg). Based on measurements obtained on the mountain during medical expeditions and during simulated climbs in hypobaric chambers it can now be calculated that a climber's arterial PO_2 (PaO_2), while climbing up near the summit, should probably be around 30–32 mmHg, $PaCO_2$ around 10–12 mmHg, maximum oxygen consumption less than one liter/min and progress very slow.

This tells us that in spite of a very strong sensation of intense effort, at extreme altitude the actual effort, in terms of power output and energy expenditure is very low. It follows that something is limiting the power output well below levels usually sustainable at lower altitudes and that an exceptionally strong mental effort is necessary to just reach such low levels of power output. It also shows us that the arterial gas tensions in humans climbing at those altitudes, which would be considered as extremely serious when observed in a patient at low altitude, are compatible with life and even (slow) motion on the mountain. Since the first ascent without bottled oxygen in 1978 several others have repeated this extraordinary feat, but more have failed, and many have died while trying. Thus, with or without bottled oxygen, it remains extremely demanding to climb as high as Mt. Everest because physiologically Mt. Everest is about as high as humans can climb. But despite considerable research the mechanisms underlying the decreased performance at high altitude are still not fully understood.

The objective of this paper is to shortly summarize what is known today on what limits exercise performance at high altitude. Moderate altitude is defined as 1500 to 3500 meters above sea level (P_IO_2 124–96 Torr); high altitude as 3500 to 5500 meters above sea level (P_IO_2 96–73 Torr) and extreme altitude as 5500 to 8848

meters or more above sea level (P_IO_2 73–53 Torr). Even though it seems obvious that the reduced inspiratory pressure of oxygen is the cause of the performance decrement it is less clear where in the organism this lack of inspired oxygen leads to such decreased function as to limit performance. For a more detailed discussion the reader is referred elsewhere (Ward et al., 1995; Roach and Kayser, 2001; Kayser, 2003).

What kind of performance is reduced at altitude?

When discussing performance we must first define what we understand by performance. Focus of this review is on physical performance, for which an adequately functioning central nervous system (CNS) is obviously necessary, but this paper does not address the important effects of hypoxia on the mental aspects of CNS functioning (Virues-Ortega et al., 2004). Physical performance depends on mechanical power generated by muscular contraction. Starting from a classical analysis of performance at the level of the energy sources used for the performance we can distinguish between very short duration explosive efforts (like jumping), short efforts (like sprinting), and endurance type efforts (like distance running). Ultimately all the energy expended for muscular contraction is derived aerobically by oxidation of substrate. However, for short periods (seconds for high energy phosphate stores ATP and phosphocreatine (PC), and minutes for lactic acid production) energy can also be made available through non-oxidative processes (anaerobic metabolism). Anaerobic metabolism is described as alactic if it concerns the high-energy phosphates ATP and PC, and lactic if the energy is made available through the production of lactic acid from glucose.

Explosive efforts

Very short duration efforts (seconds) rely almost exclusively on the rate of splitting of muscular stores of ATP and their replenishment from the PC energy buffer. In humans the capacity of this pathway can be indirectly measured by means of jumps, for example on a force platform, or maximum static or dynamic voluntary contraction force, for example using a force transducer. When looking at the maximal force or power that can be developed in various conditions the premise is that the activation of the muscles involved in the performance is maximal, that is that all motor units are fully activated, or the extent of activation does at least not vary between experimental conditions. One way to control for full activation, for example during maximum voluntary efforts against a force transducer, is the use of superimposed electrical stimulation while monitoring the force output. When activation is sub-maximal force output will increase because inactive motor units will become active upon electrical stimulation, provided the stimulation intensity is beyond the threshold for activation. This method, also known as twitch interpolation technique, has shown that voluntary activation of muscle in humans is not always maximal, and that at extreme altitude additional voluntary effort is necessary to reach maximal values (Garner et al., 1990).

Alternatively, one may circumvent voluntary activation completely by stimulating the muscle electrically and looking at contractility parameters like single or multiple twitch force development, the force vs. stimulation frequency relationship and the fatigability of the muscle upon repeated stimulation. The data of such experiments give information on the functional state of the muscle.

In theory, severe environmental hypoxia could impede ATP homeostasis. However, high-energy phosphates measured in skeletal muscle of humans show no significant decrement in hypoxia at rest or even after exhaustive exercise (Green et al., 1989). A lack of an effect of hypoxia on ATP and PC homeostasis is not only supported by findings from muscle biopsies but also from indirect measurements (maximum voluntary or electrically induced contraction force, maximum vertical jumping height, or explosive cycling peak power). These findings imply that the maximal rate of ATP hydrolysis is not influenced by hypoxia, since oxygen consumption and lactic acid production do not contribute significantly to the energy necessary during such short explosive efforts, and supports the notion that ATP and PC homeostasis are well protected, even in conditions of maximum exercise in extreme hypoxia as encountered on the top of Mt. Everest (Green et al., 1989).

Collectively the data in the literature on the effect of acute or chronic exposure to hypoxia, controlling for confounding factors like loss of muscle mass from disuse and/or malnutrition after prolonged exposure, have yielded two essential findings: firstly, explosive muscular force building capacity remains fully intact (Ferretti et al., 1990; Garner et al., 1990; Kayser et al., 1993b); and second, with increasing altitude, especially when reaching extreme altitudes around and above 8000 m, the activation of the muscles during explosive efforts may become sub-maximal (Garner et al., 1990; Caquelard et al., 2000). In other words, even though some changes have been observed (Caquelard et al., 2000) the muscle and its associated motoneurons seem to be fine, but central motor drive may decrease at extreme altitude. It follows that for explosive sports activities at altitude, performance is expected to be maintained, and for some types of sports even potentially improved because power can be maintained while air resistance is reduced.

On the other hand maximal explosive muscle power output may be diminished after climbing expeditions to very high altitudes, as well as in clinical conditions involving hypoxia that are linked to muscle wasting. But this is due to the loss of muscle mass, not to depletion of high energy energy stores or reduced rates of high energy phosphate splitting. For example, upon return from several months of exposure to extreme altitude (5300–8000 m), climbers had a drop in the instantaneous peak power (–9.8%) and the average power (–14.7%) during the push phase of a standing high jump off both feet on a force platform. The changes in power output could be fully explained by the loss of muscle mass that had occurred, since the thigh muscle cross sectional area measured by CT-scan had diminished by 11% (Ferretti et al., 1990). Thus, in spite of the maintained high-energy stores and maximum rates of ATP utilization, altitude exposure may lead to decreased power output simply because of loss of muscle mass. The reasons for the loss of muscles mass are beyond this review but seem to be related to hypoxia induced anorexia, to disuse, and possibly changes in regulation of protein synthesis (Kayser, 1994).

Sprint performance and anaerobic endurance

For efforts lasting more than a few seconds and up to several minutes, energy replenishment for ATP splitting for muscle contraction has to be provided in large part by anaerobic metabolism, pending the activation of the sluggish aerobic metabolic pathways which only become increasingly active with the duration of the effort. The anaerobic pathway used is that of the conversion of glucose into lactate yielding temporarily some ATP without the need for oxygen. Lactate production is accompanied by metabolic changes that cannot be sustained indefinitely, and muscle fatigue develops (Robergs et al., 2004).

Prolonged exposure to hypoxia leads to important changes in lactate concentrations during exercise as compared to normoxia. If in conditions of acute hypoxia lactate accumulates at lower power outputs as in normoxia while reaching similar maximum levels, it has been shown repeatedly that after prolonged periods at altitude the maximum concentration of lactate in blood is often lower as in normoxia, a phenomenon also known as «lactate paradox». The term «lactate paradox» was introduced by Hochachka based on his observations in Quechuas Indians, high altitude natives of the Andes in whom low maximal blood lactate levels were found both at altitude and upon exposure to normoxia. Reeves expanded the definition of the lactate paradox to include lowlanders, a situation *«in which blood lactate accumulation during* (submaximal) *exercise is increased on arrival at high altitude but falls with acclimatization»* (Kayser, 1996).

During graded cycle-ergometer exercise in normoxia, blood lactate concentration ([La]) depends on the type of exercise and its duration. At low work rates no increase in [La] is found, at slightly higher levels a temporary increase is seen, and during heavy exercise lactic accumulation is a hallmark. The increase in [La] is the result of a change in the balance between lactate appearance (production and washout) and lactate removal (uptake and utilization). Lactate production during the transient phase at the onset of exercise increases with exercise intensity, to be compensated for later by a corresponding increase in lactate removal, so that at steady-state exercise higher stable [La] values are observed. This equilibrium is lost during high intensity exercise when lactate production exceeds lactate removal and [La] keeps increasing with time. The increased lactate removal results from increased lactate oxidation as a substrate and from gluconeogenesis, which takes place either in organs such as the liver or in the muscles themselves («lactate shuttle»). Under certain circumstances, contracting muscles may even remove lactate produced elsewhere.

The relationship between [La] and workload is non-linear, with a steeper slope at higher workloads. This particular shape with an inflection point («lactate threshold») has been interpreted as a) a reflection of the onset of a lack of oxygen in the contracting muscle; b) an increase in the recruitment of fast twitch fibers at high workloads; c) an increased reliance on carbohydrates; d) the energy state of the cell; and e) increasing levels of circulating hormones like epinephrine. Even though severe tissue hypoxia and/or ischemia do lead to increased lactate production, there is now persuasive evidence both from animal and human studies that lactate production often occurs under strictly aerobic conditions. Therefore, the premise that an elevation of plasma [La] during exercise of increasing intensity necessarily reflects tissue hypoxia seems doubtful (Robergs et al., 2004).

Another important modulator of blood lactate during exercise in hypoxia may be the metabolic rate that can be sustained for several minutes or more. Maximal power output during incremental exercise at altitude is decreased, and so is maximal metabolic rate. Lactate appearance in blood during exercise depends on the duration, the intensity, and the volume of active muscle. In *Figure 1* $\dot{V}O_2$max and [La]max measured during a simulated climb of Mt. Everest using a hypobaric chamber (Operation Everest II or OEII) suggest a parallel drop in maximum anaerobic glycolysis and in maximum oxidative phosphorylation ($\dot{V}O_2$max) with the decrease in barometric pressure (Roach and Kayser, 2001). In hypoxia, if the high lactate levels in the non-acclimatized state are possibly due to an increase in epinephrine levels, the low lactate levels in acclimatized subjects could simply reflect diminished muscle activation during exercise with large muscle groups (Kayser, 1996).

Acclimatized muscle does not seem to lack the ability to produce lactate up to the levels seen at sea level. If the muscle mass is small and does not put a burden on mass oxygen transport, several studies have shown that acclimatized skeletal muscle can produce lactate at or even above sea level values (Lundby et al., 2000; Grassi et al., 1995). Several studies have now reported that the fraction of sea level two legged exercise maximum power output and $\dot{V}O_2$max that can be reached during exercise with just one leg is much higher at altitude than at sea level and is accompanied by much higher systemic lactate levels than reached during two-legged exercise (Kayser et al., 1993a). Summarizing, the literature suggests that the capacity of muscle to perform work is not decreased at high altitude. Rather, maximum work output is limited by diminished recruitment of active muscle.

Taken together the available evidence suggests that the increase in blood lactate during exercise at submaximal workloads in unacclimatized humans is possibly due to increased adrenergic drive of glycogenolysis, acute hypoxia inducing activation of the sympathetic nervous system (Kayser, 1996). The subsequent reduction in blood lactate with acclimatization is due to a decrease in adrenergic drive and possibly beta receptor down regulation. The reason for the reduction of the maximum blood lactate accumulation in chronic hypoxia is likely due to the decrease in maximum power output during aerobic exercise, even though some recent reports have shown normalization of maximum [La], be it at lower power as at sea level (Lundby et al., 2000). In either acute or chronic hypoxia, it seems unlikely that the Pasteur effect plays any important role. On the other hand, lactate has several roles during exercise. Apart from being a by-product of glycolysis, lactate is also a source of energy, a means to shuttle carbohydrate between organs and cells, and its hydrogen ion helps in raising or maintaining capillary PO_2 to facilitate O_2 consumption by means of the Bohr effect.

Taken together it follows that sprint performance at altitude in acclimatized humans is not compromised by anaerobic energy provision, but that aerobic energy provision, increasingly important with increasing exercise duration, may become limiting.

Endurance performance

Endurance performance is strongly affected by both acute and prolonged exposure to hypoxia. Of the three major sources of energy for work (anaerobic alactic, anaerobic lactic, and aerobic), the aerobic pathway is the most important because on a long-term basis all alactic and lactic anaerobic metabolic oxygen deficits are always followed by an aerobic metabolic debt payment. For walking, running or climbing virtually all energy necessary for work comes from the full oxidation of substrate. Thus, the performance capacity for endurance activities depends heavily on the maximum oxygen flux ($\dot{V}O_2$max) through the system from the mouth to the mitochondria. The $\dot{V}O_2$max and the fraction of $\dot{V}O_2$max that can be sustained for one or more hours (maximal sustainable $\dot{V}O_2$max) are therefore important determinants of endurance exercise capacity.

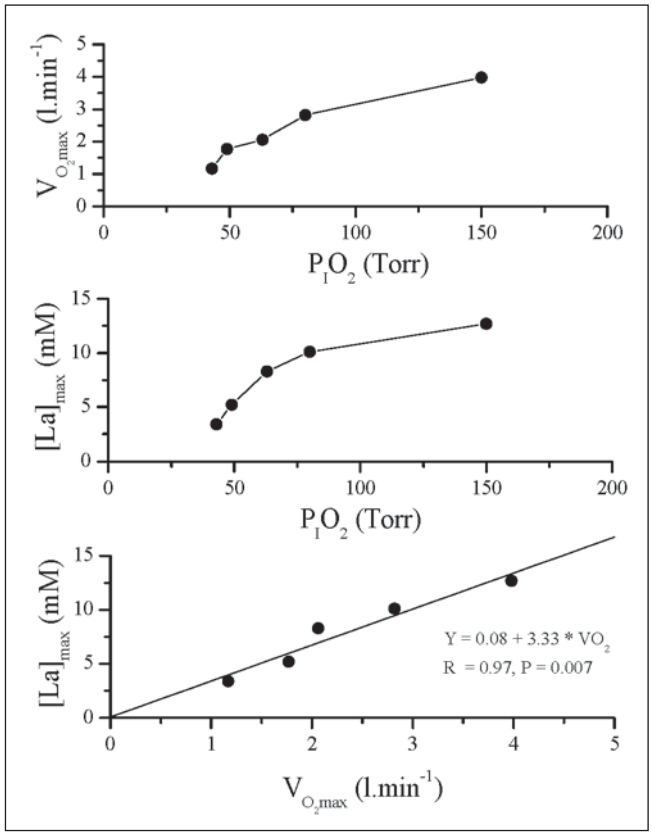

Figure 1: Average $\dot{V}O_2$max and [La]max vs. power output at the different inspiratory oxygen pressures reached during Operation Everest II, a simulated climb of Mt. Everest. In the third panel $\dot{V}O_2$max and [La]max are plotted against each other. The linear best fit suggests that in acclimatized subjects the reduction of [La]max is associated to the reduction in maximum rate of oxidative phosphorylation (adapted from Roach and Kayser, 2001).

Oxygen transport from the inspired air to the site of oxidation in the mitochondria occurs along a series of steps. The first step is convective and involves alveolar ventilation, the second is diffusional from the alveolar space through the gas-blood barrier and inter-erythrocyte plasma to the intra-erythrocyte hemoglobin, the third is again convective and involves cardiovascular blood transport. The fourth and last step is diffusion of oxygen from the capillary in to the tissues and in to the oxygen sink of the mitochondria.

By definition the oxygen consumption of the organism is equivalent to the use of oxygen in the mitochondria of the cells. Maximum oxygen consumption is thus theoretically limited by the maximum metabolic rates of the organism's total mitochondrial volume. However, simultaneous full activation of all muscles and hence all muscle mitochondrial aerobic pathways does never occur. When systemic cardio-respiratory oxygen transport is submaximal, for example when exercising with a small muscle volume, the maximum absolute aerobic metabolic rate per volume muscle is greater than when exercising with a large muscle volume when maximum cardio-respiratory oxygen transport is reached. In fact, considerable debate continues on what the limiting factors are for the maximum oxygen consumption when exercising with large muscle groups, like during running or cycling, since the muscles involved are not working at their individual maximal metabolic capacity (Kayser, 2003).

Lungs

The first step in the oxygen cascade, transport from ambient air to the alveolar space, depends on ventilation. At sea level exercise hyperpnea allows maintenance of a sufficiently high alveolar oxygen tension (P_AO_2) for the next diffusive step over the alveolar membrane. At high altitude, the partial pressure of inspired oxygen (P_IO_2) is lower than at sea level so that P_AO_2 falls, leading to a drop in arterial PO_2 (P_aO_2). This hypoxemia triggers carotid chemoreceptor firing, leading to a rise of ventilation in an attempt to elevate P_aO_2. At moderate altitude, during rest through moderate exercise a rise in alveolar ventilation can keep P_aO_2 relatively high despite the drop in P_IO_2. However, at heavier workloads and higher altitudes a dilemma may develop. Although one would expect that *any* increase in alveolar ventilation would be beneficial, the energy costs of the increased work of breathing above 60–70% $\dot{V}O_2$max may balance any gain in oxygen availability. If at sea level this does not seem to have a relevant effect, this trade-off may occur as low as 5000 m (Cibella et al., 1999). Another interesting basic physiological phenomenon occurs at the pulmonary blood-gas barrier. Since diffusion depends on the thickness of the blood-gas barrier, the barrier needs to be as thin as possible to allow for efficient gas exchange. On the other hand, it must also be able to withstand the high stresses that ensue when the pulmonary capillary pressure rises on exercise and when flow rates are high. An increase in thickness of the blood-gas barrier will decrease diffusional oxygen transport. A third dilemma involves maximum cardiac output during exercise at high altitude. The Fick equation [$\dot{V}O_2$ = cardiac output ($C_aO_2 - C\bar{v}O_2$)] says that at a given arterial oxygen content (C_aO_2), in order to keep $\dot{V}O_2$max as close as possible to that achieved at sea level, one has to keep cardiac output as high as possible (in the face of unchanging oxygen extraction). However, since the pressure gradient across the blood-gas barrier is reduced, a shortened blood transit time as a consequence of increased cardiac output may not allow time for equilibration of the pulmonary capillary blood oxygen partial pressure with that in the alveoli (Wagner, 2000). Highly trained athletes who have high cardiac outputs and therefore short pulmonary capillary transit times show considerably more arterial desaturation upon hypoxic exercise compared to untrained subjects (Ferretti et al., 1997). With acclimatization hemoglobin concentration typically rises, increasing C_aO_2 and allowing a lower cardiac output for a given $\dot{V}O_2$ which ameliorates to some extent the effects of arterial oxygen desaturation. Hemoglobin concentration, blood viscosity, and O_2 affinity of hemoglobin all can affect oxygen uptake.

It remains to be investigated if the high rates of ventilation, putting a burden on the respiratory muscles possibly leading to muscle fatigue and weakness may be an additional limiting factor (Deboeck et al., 2005; Cibella et al., 1996; Cibella et al., 1999).

Cardiovascular

Perhaps the most important observation about the heart at high altitude is that its function is well preserved, on the condition that it was healthy before going to high altitude. Cardiovascular regulation certainly changes with exposure to hypoxia, but contrary to what one would expect for such an aerobic organ, known to suffer greatly from acute focal ischemia, the heart performs well even at the summit of Mt. Everest, as was shown by the invasive measurements obtained during Operation Everest 2 (OEII) (Reeves et al., 1987). The finding of a lower peak heart rate in chronic hypoxia has been consistently confirmed. In contrast, during acute hypoxia some studies show no depression of peak heart rate, while others show a significant decrease. Why peak heart rate falls with sustained hypoxia, and why the response to acute hypoxia is so variable is not known, even though increased parasympathetic activation was found to play a role (Boushel et al., 2001). One explanation for the individual variability may be different training status between the subjects of the studies. A high degree of physical fitness at sea level is associated with a larger decrement in peak heart rate and with hypoxia (Ferretti et al., 1997). During submaximal exercise in hypoxia the heart rate is elevated above levels seen for the same workload at sea level. Stroke volume is initially slightly lower during submaximal and maximal exercise at altitudes from 3000 m to 5000 m (P_IO_2 103–78 Torr), and returns toward but not to sea level values with acclimatization. The decrease in myocardial work as a consequence of the drop in peak heart rate and stroke volume could, in theory, protect the myocardium from extreme hypoxemia. However, myocardial blood flow rises markedly during exercise in severe, acute hypoxia and the rise resulting in an increase in oxygen delivery that nearly compensates for the hypoxemia (at least down to an F_IO_2 of 0.10), such that the myocardium appears well protected. Another possible mechanism for the reduction of stroke volume early in acclimatization is the reduction in total blood volume due to the contraction of the plasma volume. However, acute expansion of plasma volume with dextran infusion in subjects exercising in chronic hypoxia results in an increase in stroke volume and a decrease in maximal frequency but leaves cardiac output and $\dot{V}O_2$max the same (Robach et al., 2000).

Recent data on the effects of sildenafil on the pulmonary arterial hypertension induced effects on the right heart and pulmonary circulation suggest some role for changed interplay between the heart and lungs during heavy exercise at high altitude, since performance was increased when pulmonary arterial pressure was reduced (Ghofrani et al., 2004).

Collectively the available evidence suggests that the heart is fine during endurance type exercise in acute and chronic hypoxia, but that it is not solicited as much as in conditions of normoxia, because of a reduction of muscle recruitment. At all times it seems as if cardiac output is simply maintained commensurate to oxygen transport needs which are set by muscle recruitment induced muscular energy expenditure that at altitude apparently never outstrips heart reserve.

Only in chronic (like life time) conditions the (right) heart may get into trouble from the hypoxia induced pulmonary arterial hypertension, as evidenced by right heart failure described in infants and adults living at high altitude (Ge and Helun, 2001).

The last step in the oxygen transport chain involves the delivery of oxygen to cells. Oxygen, unloaded from hemoglobin, diffuses through plasma and the capillary wall into the myocyte, then via myoglobin to the mitochondria. Since oxygen delivery is the product of C_aO_2 and blood flow, any strategy that increases C_aO_2 with the same blood flow will increase the oxygen available for diffusion into the muscle cell. Initially, plasma volume contracts in response to hypoxia, with only a minimal rise over two months

at the same altitude (4300 m). This initial 10 to 15% reduction in plasma volume results in an increased hemoglobin concentration and hence C_aO_2. An actual increase in total red cell mass occurs after several weeks of hypoxia, secondary to the stimulation of erythropoiesis by hypoxia. Finally, muscle oxidative capacity and structure play a role in delivery of oxygen for muscular exercise.

Endurance performance capacity depends on aerobic metabolism and hence on the maximum sustainable oxygen uptake. In a moderately trained subject at sea level the maximum sustainable oxygen uptake is typically located at about 80% $\dot{V}O_2$max, midway between the lactate threshold and $\dot{V}O_2$max. The combination of a high $\dot{V}O_2$max and a high maximum sustainable oxygen uptake is thus a good physiological basis for endurance exercise at sea level. It is well known that $\dot{V}O_2$max decreases as P_IO_2 falls. As shown in *Figure 2* the drop in $\dot{V}O_2$max becomes progressively steeper at lower P_IO_2. The $\dot{V}O_2$max declines ~1% per 100 m elevation gain above 1500 m.

After the initial decrease of $\dot{V}O_2$max with acute hypoxia, further exposure has a small influence on $\dot{V}O_2$max. For example, during a 5 week sojourn at 5050 m $\dot{V}O_2$max initially fell 47%, followed by partial recovery of 4 to 8% after 15 and 35 days, respectively. Upon descent to sea level, $\dot{V}O_2$max was 92% of the pre-expedition level and did not recover to pre-expedition values for at least five weeks (Grassi et al., 1996). However, endurance time at a given submaximal workload rises with acclimatization. The elevation of endurance time is not strictly due to enhanced oxygen delivery. The rise in C_aO_2 (secondary to elevated hemoglobin) is balanced by a drop in cardiac output, the net effect being little change in oxygen delivery. The mechanisms for the rise in endurance time with acclimatization during a prolonged stay in chronic hypoxia, or for the rise in $\dot{V}O_2$max during prolonged hypoxia are not known.

What limits $\dot{V}O_2$max at sea level has received considerable attention in the past and continues to be a field of vivid debate. It is now generally accepted that limitation to $\dot{V}O_2$max in hypoxia is multifactorial. Today's existing models approach the problem from different viewpoints and necessarily yield different insights (for a comparison see Roach and Kayser, 2001). However, most models fail to take fully into account the determining factor of the volume, intensity and duration of muscle recruitment, which by definition sets the demand for oxygen of the system.

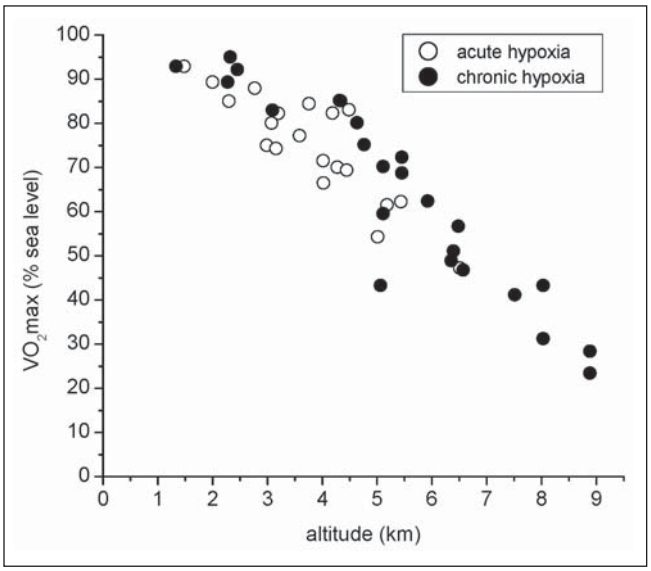

Figure 2: The decrease in $\dot{V}O_2$max as a function of altitude expressed in % of sea level control compiled from the literature. Symbols represent average data points from different papers. Open symbols are acute hypoxic exposure and closed symbols chronic exposure (adapted from Roach and Kayser, 2001).

Recruitment

Any voluntary physical activity begins with a conscious decision that leads to the activation of the motor cortex and to the orderly spatial and temporal recruitment of motor units in the muscles. The activity is ended with the de-recruitment of motor units. This is also valid at the end of maximum exercise when the end of effort is again volitional and a forced conscious decision to stop precedes it, but it is unknown what forces the off-switch of recruitment at exhaustion although sensation of exertion certainly plays a role. The end of effort is again volitional and a (forced) conscious decision precedes it. Central command in the motor cortex is perceived as a sense of effort, and exercise is volitionally terminated when the sense of effort and other sensations like muscle pain become more intense than is tolerable. Thus, the perception of effort is an important factor that limits exercise. However, the sensory aspects of exercise are not widely appreciated, at least in part because of a reluctance to accept subjective data (Jones and Killian, 2000). A simple example is an incremental exercise test on a cycle ergometer when a subject pedals at increasing power outputs and at a certain maximum output cannot maintain the effort anymore and ultimately decides to stop cycling. The majority of subjects will tell you that they «simply had to stop». This is usually referred to in the literature as «volitional exhaustion» and this point is generally believed to coincide with «true» maximum metabolic and cardiovascular capacity.

The CNS as limiting factor

At the cessation or reduction in intensity of heavy exercise the obligatory decision to stop or reduce the effort is conscious, and thus likely occurs at cortical levels, probably forced by sub-cortical brain circuitry. But what provides the input to the CNS leading to the forced decision to end an exercise? Noakes proposed the existence of a functional entity dubbed a «central governor», which would limit exercise performance (Noakes et al., 2001). Such a governor would prevent the recruitment of muscle mass beyond levels of intensity and duration where potential damage would occur to the heart or other vital parts of the organism. Even though the CNS as the ultimate limiting factor would appear obvious, the notion of a central governor that limits exercise to protect the integrity of the organism remains hypothetical.

The various inputs during exercise at sea level and in hypoxia are probably the same, but their relative importance and central processing may be altered by hypoxia. For example, the sensation of breathlessness felt at a ventilation of 75 l/min during a standard exercise challenge at sea level was reduced by 35% after return from a four week sojourn at 4000 m, an effect that lasted at least six weeks (Wilson et al., 1993). As another example, in hypoxia, but not in normoxia, signs of fatigue of the diaphragm are seen on cessation of exhaustive large muscle group exercise (Kayser et al., 1993a; Cibella et al., 1996).

Further support for a central limitation to exercise comes from whole body exercise studies carried out during OEII. During peak exercise at the highest altitudes, arterial oxygen saturation fell to 40%, and P_aO_2 dropped as low as 26 Torr. The clinical findings of near unconsciousness at the end of exercise, coupled with the extreme hypoxemia suggests that the brain may well have been the critical limiting organ to exercise performance. During such severe hypoxemia breathlessness was expected to be an exercise limiting symptom, however, both breathlessness and leg fatigue were graded equal and maximal. These symptomatic observations taken in conjunction with the absence of metabolic fatigue in the exercising legs, suggest that a failure of the CNS to drive the locomotor apparatus rather than any muscular metabolic inhibition is what limits performance.

Based on data from the OEII study, Bigland-Ritchie and Vollestad hypothesized that a maximally stressed respiratory system could, via the central nervous system, limit the motor drive to active locomotor muscle groups before their full potential was reached

(Bigland-Ritchie and Vollestad, 1988). For a given % $\dot{V}O_2$max the respiratory system is stressed more during heavy exercise in hypoxia than in normoxia. A subsequent report supports the notion of an interaction between respiratory muscle fatigue and limitation to exercise in hypoxia. Five subjects cycled to exhaustion at 75% $\dot{V}O_2$max in normoxia and after one month at 5050 m (Cibella et al., 1996). At altitude, the absolute work load was 24% below sea level values. In spite of the reduced load, time to exhaustion was only 55% of the sea level value. Although mechanical power output of the locomotor muscles on the cycle ergometer and $\dot{V}O_2$ were lower at altitude, the ventilatory requirement rose. The authors argued that there were indirect indications pointing to possible respiratory muscle fatigue, including a drop in tidal volume coupled to a rise in breathing frequency. In addition, they observed negative inspiratory gastric pressure swings that are consistent with a paradoxical upward movement of the diaphragm during inspiration, which supports the presence of diaphragm fatigue. In one subject, just prior to exhaustion, a decrease in the tidal volume to inspiratory time ratio suggested a drop in motor drive to the respiratory muscles. Fatigue, or the dramatic continuous increase in ventilatory drive during cycle exercise at 75% of $\dot{V}O_2$max, could thus provide an input to the central nervous system leading to a decrease in central drive to the active locomotor muscles before those muscles develop exercise-terminating peripheral metabolic fatigue. In hypoxia, the legs do not show signs of peripheral metabolic fatigue. In fact, when working muscle volume is reduced (eg. one-legged exercise), the maximum power output of the working muscles can reach sea level values, and only then does peripheral metabolic fatigue occur.

On the other hand, an experiment performed at 5200 m does not seem to support a role for respiratory muscle fatigue leading to a central limitation of exercise in hypoxia (Savard et al., 1996). Acclimatized subjects at 5200 m performed repeated maximal isometric voluntary contractions with the forearm flexors before and during exhausting bicycle exercise with and without 4% inspiratory carbon dioxide. The addition of carbon dioxide caused an elevation in ventilation at peak effort. The additional respiratory muscle work did not alter the force generated by a maximal voluntary contraction of the forearm muscles during peak effort. The authors concluded that central drive to the respiratory muscles or locomotor muscles was intact, and had not changed with the increased work of breathing during inhalation of carbon dioxide.

Another hypothetical route to a ventilation-engendered central limitation to exercise emerged from observations made on soldiers suffering from high altitude pulmonary edema. Paintal suggested that hypoxic pulmonary arterial constriction at high altitude, combined with an exercise-induced additional rise in pulmonary arterial pressure and flow, might activate pulmonary juxta-capillary receptors (Paintal, 1995). In turn, the juxta-capillary receptors, which are sensitive to pressure as well as interstitial edema, would via the vagus give rise to dyspnea and could by a reflex mechanism limit central motor drive. To date there are no data to directly support this hypothesis even though the recent reported increase in exercise performance under sildenafil would be in favor (Ghofrani et al., 2004).

An interesting phenomenon is that increasing the inspiratory oxygen tension at the point of exhaustion from heavy exercise in hypoxia has now been repeatedly reported to allow the continuation of exercise, sometimes even to sea level proportions (Kayser et al., 1994; Calbet et al., 2003).

Thus, the origin of the signals leading to the cessation of the central motor drive at exhaustion during heavy large muscle group exercise in hypoxia remains unclear. Possible candidates controlling the signal to stop exercise include arterial O_2 desaturation with exercise causing marked central nervous system hypoxia, other factors acting on the respiratory and/or other higher nervous centers, with or without contribution of fatigued respiratory muscles, or the effects of pulmonary hypertension. The proposed mechanism of early central nervous limitation to exercise in hypoxia is compatible with the absence of signs of peripheral metabolic fatigue and submaximal cardiac output at the end of exhausting maximum exercise with large muscle groups in hypoxia.

Conclusions

Contrary to maintained explosive power and sprint performance, endurance performance is diminished in hypoxia. Even though it is clear that this is due to the reduction in inspiratory pressure of oxygen the mechanisms for this decrement remain to be elucidated. As such the locomotor system seems to be well preserved, just as the metabolic machinery for energy provision for muscle contraction, but apparently these cannot be solicited to the same extent as compared to low altitude. A reduction in the maximally sustainable recruitment of large volumes of muscle by the central nervous system appears to be central but how this reduction is brought about remains an open question.

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