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Exercise physiology: exercise performance at altitude

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This review explores recent advances in the etiology of exercise intolerance (classically defined by a reduced maximal or peak oxygen uptake) in lowlanders at high altitudes, focussing on sites of physiological-system limitation and how these may differ in highlanders. The traditional opinion of impaired oxygen delivery along a convective-diffusive cascade between lungs and exercising-muscle mitochondria remains relevant but an oversimplification. Thus, developments in genomics, proteomics and metabolomics are providing an exciting, expanded perspective of exercising-muscle function. However, factors such as ascent profile, altitude sojourn, training status, ethnicity, genetics and development present interpretational challenges. Also, while animal models can be useful proxies for human function because they allow a greater degree of invasive interrogation, species differences can limit their applicability. Finally, assessment of exercise performance at altitude requires rigorous application of exercise intensity, through key demarcators such as the lactate threshold, critical power and W′ — each of which are altitude-dependent.

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Introduction

This article focusses on major recent developments relating to the system adaptive responses during high altitude (HA) sojourns in healthy adult lowlanders in the context of exercise performance and tolerance, and their congruences with and departures from those of highlanders. Interventions for potential performance enhancement at HA (e.g. training; O_2, carbohydrate or nitrate-related supplementation; acetazolamide; pulmonary vasodilators) will not be addressed. Providing a consistent picture for acclimatizing lowlanders can be problematic, because of variables such as ascent profile, altitude sojourn and training status. Nonetheless it has long been recognised that exercise tolerance is compromised when lowlanders ascend to HA, even for prolonged sojourns, as judged by a reduced maximal O_2 uptake ($\dot{V}O_2$max) or its more-easily measured proxy, peak $\dot{V}O_2$ ($\dot{V}O_2$peak) [1]. And whether or not highlanders uniformly express higher $\dot{V}O_2$max values relative to lowlander counterparts at HA similarly depends on ethnicity, training status and also genetic and developmental factors (reviewed in Refs. [2,3•,4••]). It should be recognized, however, that exercise intolerance can also result at submaximal work rates (WRs), if sufficiently prolonged, and involving mechanisms that may differ from those limiting $\dot{V}O_2$max; that is, exercise tolerance is intensity-dependent.

Defining intensity using physiologically-defensible criteria [1], WRs for which there is no sustained metabolic acidosis (i.e. <lactate threshold (θ_L)) are highly sustainable (*moderate*), with tolerance being limited not by O_2 provision but by substrate availability. Above θ_L, there is a WR range whose upper limit is set by critical power (CP), for which arterial [lactate] and $[H^+]$ are increased but can stabilize (*heavy*). An eventual $\dot{V}O_2$ steady-state can be attained but at values greater than predicted from sub-θ_L exercise. While exercise is still sustainable, anaerobiosis and aerobic inefficiency impose appreciably-greater carbohydrate utilization costs with muscular system and ventilator system stress, predisposing towards earlier exercise cessation. For >CP WRs (*very heavy*), [lactate], $[H^+]$ and $\dot{V}O_2$ increase throughout the exercise, more markedly the higher the WR and therefore achieving the tolerance limit at $\dot{V}O_2$max more rapidly; that is $\dot{V}O_2$max is not associated with a unique ‘maximal’ WR but a range of supra-CP WRs.

Causes of $\dot{V}O_2$max reduction at HA

The determinants of $\dot{V}O_2$max at SL are multifactorial and still debated. Regardless, the compromised environmental O_2 availability at HA imposes additional systemic challenges to muscle O_2 consumption ($\dot{Q}O_2$) during exercise with regard to the ability to (a) maintain convective-diffusive O_2 delivery from lungs to working muscles and muscle fibres and (b) deliver and utilize O_2 appropriately within muscle mitochondria [5,6]. Given the technical constraints of direct investigations into the relative contributions of these mechanisms at different altitudes, valuable insight has been gained from modelling analyses, as recently addressed [6]. For example, in the context of the 1978 Habeler-Messner Everest ascent without supplemental O_2 has been used to illustrate how small changes in individual components of the O_2 cascade have the potential to conflate into appreciable performance changes [6].

Ventilation and dyspnoea

Available evidence suggests that ventilation ($\dot{V}E$) in lowlanders at HA (Mt Everest, up to 7950 m) does not typically limit $\dot{V}O_2$max, that is peak $\dot{V}E$ does not approach respiratory-mechanical limits when these are actually determined at HA [DZH Levett, PhD thesis, University College London, 2014], rather than being assumed to equal SL values (Ev-K2-CNR Pyramid Laboratory, Lobuche; 5050 m) [7]. Thus, despite peak $\dot{V}E$ being higher at HA (presumably reflecting increased carotid chemoreceptor activation), it did not approach the limiting proxy of the maximum voluntary ventilation (MVV) that was increased to a greater degree (presumably consequent to reduced inspired gas density tending to reduce work of breathing); that is breathing reserve (peak $\dot{V}E - MVV$) was increased. Whether the spontaneous expiratory flow-volume curve is similarly not limiting awaits investigation. Regardless, the associated degrees of dyspnoea can be limiting, presumably reflective of factors such as respiratory muscle work, respiratory muscle fatigue and an amplifying dyspnoeagenic effect of hypoxia at the carotid chemoreceptors [7].

Pulmonary gas exchange

The reserve to recruit and/or distend pulmonary capillaries during maximal exercise has been demonstrated to constrain the HA-related decrement in $\dot{V}O_2$peak in a small cohort ($n = 7$) of acclimatized lowlanders (Mt Everest Base Camp (EBC); 5150 m, ~40 days) [8]. That is, two individuals with larger pre-exercise to immediate post-exercise increases in lung diffusing capacity for carbon monoxide (D_LCO), alveolar-capillary membrane conductance (D_MCO) and pulmonary capillary blood volume (Vc) at HA expressed smaller HA-related decrements in $\dot{V}O_2$peak than the remaining five individuals for whom exercise-related pulmonary capillary recruitment and distension was essentially constrained. The importance of accommodating high pulmonary blood flows for exercise tolerance at HA without excessive increase in pulmonary arterial pressure (PAP) was further underscored in lowlanders and Sherpa [9]. Despite little difference in group-mean $\dot{V}O_2$peak at HA (Ev-K2-CNR Pyramid Laboratory, Lobuche; 5050 m), D_LCO was directly correlated with $\dot{V}O_2$peak across individuals while exercise pulmonary vascular resistance demonstrated an inverse correlation.

An additional influence on alveolar gas-exchange efficiency (the alveolar-arterial O_2 difference ($AaDO_2$)) and exercise tolerance at HA relates to intrapulmonary arteriovenous anastomoses (IPAVA; right-to-left shunts). Two studies have demonstrated that hypobaric hypoxia (unlike normobaric hypoxia) does not accentuate the SL increase in IPAVA blood flow ($\dot{Q}_{IPAVA}$; transthoracic agitated saline contrast echocardiography) with increasing WR [10,11]. Although resting $\dot{Q}_{IPAVA}$ was greater at HA than at SL, in one study (Ev-K2-CNR Pyramid Laboratory; 5050 m, Lobouche), no further increase was evident for submaximal WRs despite more marked increases in cardiac output ($\dot{Q}_T$) and PAP [10]. In the other (Mt Chacaltaya, Bolivia; 5260 m), there was a tendency for $\dot{Q}_{IPAVA}$ to increase with WR but values were less than for SL; interestingly, this was not reflected in a smaller $AaDO_2$ [11]. The difference in $\dot{Q}_{IPAVA}$ response between these two studies is unclear, although one used supine cycling [10] and the other upright cycling [11]. This lack of $\dot{Q}_{IPAVA}$ increase with exercise was argued not to reflect an influence of saline contrast microbubble instability or lifetime, based on modelling predictions, with putative mediators including hypobaria *per se* (exercise $\dot{Q}_{IPAVA}$ was attenuated also with hypobaric normoxia) [11], concomitant increases in ventilation-perfusion mismatch and diffusion limitation offsetting $\dot{Q}_{IPAVA}$ increase [11] and pulmonary vascular remodelling [10].

Arterial O_2 transport

Haemoglobin

A role for splenic contraction in O_2 transport during exercise in lowlanders at HA (Khumbu Valley; 3440 and 4240 m) appears unlikely, at least based on small-muscle exercise [12]. Thus, while acute normobaric hypoxia can result in splenic contraction and erythrocyte mobilisation, this was not observed at HA despite a demonstrable splenic response to direct adrenergic receptor stimulation (phenylephrine infusion).

Recently, Tibetan HA residents (>4000 m) having haemoglobin (Hb) levels within the normal SL range (c.f. the characteristically elevated [Hb] in Andean highlanders and lowlanders sojourning at HA) were reported to have $\dot{V}O_2$peak values that were higher than for those having an elevated [Hb] [13]; which contrasts with the relative insensitivity of $\dot{V}O_2$peak to [Hb] in lowlanders at HA [5,14]. This performance advantage was associated with higher peak $\dot{Q}_T$ and muscle O_2 diffusing capacity and lower arterial PCO_2 but unrelated to pulmonary gas exchange indices. These observations underscore the importance of adaptive interaction among individual elements of the O_2 cascade in setting aerobic capacity in HA populations.

Cardiac output

Indirect evidence for a cardiac limitation at peak exercise in lowlanders at extreme HA (Mt Everest South Col;

7950 m) was provided by the demonstration in 3 of 5 mountaineers of a flattened O_2 pulse (=$\dot{V}O_2$/heart rate or SV × arterio-mixed venous O_2 content difference) profile with a compensatory further tachycardia as the considerably compromised $\dot{V}O_2$peak (~40% of SL values) was approached during incremental exercise [DZH Levett, PhD thesis, University College London, 2014]. This could be consistent with a stroke volume (SV) limitation possibly consequent to constraints on myocardial O_2 supply, although a limitation of muscle O_2 extraction cannot be ruled out.

How $\dot{V}O_2$max in lowlanders at HA (White Mountain; 3800 m) might be influenced by a compromised SV and left ventricular (LV) filling (reflecting plasma volume reduction (reviewed in Refs. [14,15]) and increased pulmonary vascular resistance (PVR) (reviewed in Ref. [16]) has most recently been explored with plasma volume expansion to SL values and sildenafil administration to reverse hypoxic pulmonary vasoconstriction [17••]. Each condition restored resting LV end-diastolic volume and SV (although less markedly with sildenafil), with their submaximal exercise responses were unchanged from SL (technical considerations precluded LV monitoring at maximal exercise). However, HA $\dot{V}O_2$peak was not increased. Whether this lack of influence of LV filling on performance extends to higher altitudes (which the authors speculated might be a factor in reconciling earlier discrepant findings) or to highlanders awaits investigation, as does right ventricular dysfunction (e.g. consequent to increased afterload) (reviewed in Refs. [15,16,18]).

Skeletal muscle O_2 transport

Muscle blood flow

Little is known about how chronic or lifetime HA exposure affects the preferential redistribution of $\dot{Q}_T$ to the working muscles during exercise, and therefore convective O_2 transfer rates. However, it is well established that acute normobaric hypoxia augments the muscle blood flow ($\dot{Q}_M$) response to exercise through local vasodilatory mediators such as endothelial-derived nitric oxide (NO) and prostaglandins with circulating epinephrine, although modulated by a degree of hypoxia-induced sympathetic vasoconstrictor restraint; a strategy to preserve O_2 delivery at levels appropriate for current metabolic requirements (reviewed in Refs. [19,20]). Indeed, HA-induced muscle sympathetic nerve activity has been demonstrated (microneurography; common peroneal nerve) in acclimatizing lowlanders (El Alto, Bolivia, 4100 m; 40 days) and to a similar degree in Aymara highlanders [21]. Whether $\dot{Q}_M$ at peak WRs is predictable from these submaximal responses or not, and therefore whether it could potentially limit $\dot{V}O_2$max, is unclear. Also uncertain is whether HA exposure promotes a degree of muscle arterio-venous shunting which, as for the lungs, would compromise mitochondrial oxygenation [6].

The possibility should also be considered that whether, under the conditions of exacerbated ventilatory drive at HA, the perfusion requirements of the respiratory muscles 'take preference' over those of the locomotor muscles (respiratory steal) consequently compromising $\dot{Q}_M$ (via sympathetic vasoconstriction) and leading to premature locomotor-muscle fatigue [22]. Available evidence suggests this is not the case, however. Thus, in lowlanders (Cerrode Pasco; 4350 m), intercostal and vastus medialis muscle O_2 saturation (S_MO_2) (a non-invasive marker of muscle oxygenation; near-infrared spectroscopy (NIRS)) decreased similarly during incremental exercise, with the former being lower than the latter at peak WRs, and intercostal and vastus medialis muscle [Hb] (a marker of muscle perfusion) increased with WR [23]. Similar profiles were seen in highlanders.

A suboptimal regional matching of $\dot{Q}_M$ to $\dot{Q}O_2$ also has the potential to limit $\dot{V}O_2$max at HA, compromising mitochondrial oxygenation and predisposing to anaerobiosis [6]. For normobaric hypoxia, regional dispersions of $\dot{Q}_M$ and $\dot{Q}O_2$ in vastus lateralis (via indocyanine green dye appearance and tissue oxygenation NIRS-based measurement, respectively) increased with WR but $\dot{Q}O_2/\dot{Q}_M$ remained essentially unchanged [24]. This would be consistent with local control of $\dot{Q}_M$ in accordance with regional metabolic demands. Whether intramuscular $\dot{Q}O_2/\dot{Q}_M$ distributions are affected at HA is unknown, although a multi-compartment model analysis based on data from the Operation Everest II expedition showed that at peak exercise regional mitochondrial PO_2 could vary widely consequent to $\dot{Q}O_2/\dot{Q}_M$ heterogeneity, although this became less marked as mitochondrial metabolic capacity was caused to be increasingly greater than the capacity to deliver O_2 [25].

Microcirculatory flow may also be an important determinant of performance through its effects on tissue oxygen delivery. Lowlanders have been demonstrated to have reduced microcirculatory flow at high altitude [26]. In contrast microcirculatory function was preserved in Sherpa, at the same altitude (5300 m) [27]. These differences may contribute to the superior exercise performance of Sherpas at altitude.

Muscle diffusing capacity

It has been reported that Aymara highlanders have a lower leg $\dot{Q}$ and O_2 extraction at peak exercise, with a consequently lower leg $\dot{V}O_2$max than acclimatizing lowlanders (El Alto, Bolivia, 4100 m; 40 days) [28]. As the O_2 lower extraction was associated with a lower muscle O_2 conductance (leg blood flow × femoral arterio-venous PO_2 difference), it was suggested that Aymara highlanders are more prone to muscle O_2 diffusion limitation than lowlanders. Despite this, interestingly, the Aymara maintained a relatively high arterial oxygenation, which was ascribed to D_LO_2.

Muscle energetics

Recent muscle proteomic and metabolomics studies have provided insight into the controversy regarding substrate oxidation responses to acute and chronic HA in lowlanders and highlanders, although by no means resolving it. The degree of hypoxia and the duration of exposure are important factors when interpreting metabolic changes at altitude. For example after reasonably short exposures to hypoxia (EBC; 5300 m, 19 days), uncoupling protein 3 (UCP3) expression was unchanged (although with a trend towards UCP3 upregulation: see Section 'Muscle mass') suggesting unchanged mitochondrial efficiency [29]. However, after more prolonged exposure at a lower altitude (Jungfraujoch; 3454 m, 28 days), mitochondrial respiratory capacity (decreased tricarboxylic acid cycle (TCA) and oxidative phosphorylation (OxPhos) enzyme levels) has been demonstrated to be downregulated in lowlanders, but with improved mitochondrial coupling efficiency that correlated with HA $\dot{V}O_2$max [30]. Furthermore after chronic exposure to more extreme altitude (66 days, including Summit ascent) [UCP3] was decreased, suggesting increased mitochondrial ATP efficiency although in the face of a suppression of electron transport (cytochrome c oxidase (COX) activity) [29]. Additionally, the observed decrease in β-hydroxyacyl-CoA-dehydrogenase (HOAD) activity was consistent with β-oxidation downregulation [31], which could improve the efficiency of mitochondrial O_2 utilization via preferential carbohydrate metabolism [29]. These acclimatizing responses were suggested to decrease mitochondrial $\dot{Q}O_2$ in parallel with decreased O_2 supply, to preserve or even increase metabolic efficiency [29]. The demonstration that peroxisome proliferator-activated receptor α (PPARα) expression was increased, which may favour a switch towards mitochondrial uncoupling and greater fatty acid oxidation with consequent glycogen sparing, is challenging to this interpretation [29]. It may be that PPARα has other important regulatory actions at HA such as regulating mitochondrial function [29,32]. Proteomic analysis on the same subjects provides further support for the downregulation of aerobic metabolism with a decrement of the TCA cycle enzymes regulating the fate of α-KG (IDH2,OGDH) and fatty acid metabolism (ACADVL, ACADS) in the early but, particularly, in the late phase of acclimatization [33]. Furthermore, increases in heat shock proteins (HSPs) such as HSC70 belonging to the heat-shock 70 kDa family were observed. These HSPs are involved in chaperone-mediated mitochondrial autophagy and may partially underlie the observed reduction in mitochondrial density (see below) [33].

The importance of mitochondrial adaptation to hypoxia was further emphasized in the study of Chicco *et al.* evaluating respirometry, metabolomics and proteomics in lowland residents exposed to high altitude (5200 m) [34]. They reported a rise in the resting phosphorylation potential enhancing the efficiency of oxidation of long-chain acylcarnitine. This directs higher amounts of muscle glucose toward pentose phosphate and one-carbon metabolism pathways that, in turn, support cytosolic redox balance.

Recently respirometry, genetics and metabolomics were compared between lowlanders and Sherpas exposed to a controlled ascent to 5300 m [35••]. Compared with lowlanders, Sherpa demonstrated a lower capacity for fatty acid oxidation in skeletal muscle biopsies, along with enhanced efficiency of O_2 utilization, improved muscle energetics, and protection against oxidative stress. This adaptation appeared to be related, in part, to a putatively advantageous allele for the PPAR A (PPARA) gene, which encodes for PPARα and which was enriched in the Sherpa compared with the lowlanders. This was argued to favour improved metabolic efficiency and O_2 conservation [36].

The extent to which adaptive restoration of mitochondrial energetics might confer performance advantage(s) at HA is, however, unclear [33,34]. One possibly detrimental effect of a substrate switch to carbohydrate is that tolerance at supra-θ_L WRs could be compromised; that is any gains in mitochondrial efficiency being outweighed by constraints on obligatory anaerobic glycolysis $>\theta_L$.

Mitochrondrial density

The reduction in muscle mitochondrial density that occurs in lowlanders acclimatizing to HA is a further factor compromising exercise capacity, is likely to have a complex aetiology and may reflect metabolic adaptation to hypoxia (reviewed in Ref. [38]). For example, after relatively short exposure to HA (EBC; 5300 m, 19 days), mitochondrial density is unaffected but there was a trend towards UCP3 upregulation that could potentially protect mitochondria (particularly the inter-myofibrillar population in which UCP3 is more highly expressed) from excessive reactive oxygen species (ROS) production [29] (see Section 'Muscle energetics'). However on more prolonged exposure to extreme altitude, mitochondrial density is decreased by more than 30%, with preferential loss of the subsarcolemmal mitochondria rather than the inter-myofibrillar mitochondria and was accompanied by downregulation of PPAR γ coactivator 1α (PGC-1α). This was suggestive of downregulation of mitochondrial biogenesis, coupled with mitophagy and chaperone-mediated autophagy [33].

Correction of the negative energy balance typical of HA ascent (Jungfraujoch; 3454 m, 28 days), (maintenance of SL habitual physical activity and diet) was associated with preserved body mass, fat-free mass (FFM) and skeletal muscle fibre cross-sectional area with mitochondrial density actually being increased (preferentially for inter-myofibrillar mitochondria) [37]. Despite this, there was only a nonsignificant trend towards a $\dot{V}O_2$peak increase, ascribed to a concomitant Hb mass increase. The mechanisms underlying this increase were unclear, there being no change in COX, mitochondrial mass-specific respiration, mitochondrial efficiency or antioxidant content (catalase, mitochondrial-specific superoxide dismutase 2). Whether $\dot{V}O_2$peak might be more convincingly affected at higher altitudes and/or for more prolonged sojourns awaits investigation.

Lower mitochondria densities have also been reported in Sherpa, relative to lowlanders at HA (e.g. [35••]). Whether decreased mitochondrial density, either in Sherpa or in acclimatizing lowlanders, reflects simple tissue deterioration or metabolic adaptation has yet to be resolved [38].

Muscle mass

Sarcopenia is a further challenge to $\dot{V}O_2$max in lowlanders undergoing prolonged HA sojourns, with putative mediators including oxidative stress, chronic inflammation and mitochondrial dysfunction. In lowlanders at HA (EBC, 5300 m; 8 weeks), several of whom completed Summit ascents, associations were identified between FFM loss and increased circulating biomarkers of oxidative stress (4-hydroxynonenal), inflammation (interleukin 6, IL-6), NO bioavailability (nitrite) and appetite control (glucagon-like peptide 1, GLP-1) [39]. Multivariate analysis revealed that increases in [GLP-1], [nitrite] and [insulin] were significant predictors of FFM loss. The association between FFM loss and [nitrite] was suggested to be compensatory for muscle efficiency improvement, with GLP-1 and nitrite-NO pathways being potential targets for alleviating HA sarcopenia and improving exercise performance.

Changes in circulating myokines in lowlander mountaineers on a climbing expedition (Alps; 3000 m, 14 days) were also consistent with a downregulation of myogenesis. Thus, an increase in IL-6 post-expedition versus pre-expedition was accompanied by an increase in myostatin (an inhibitor of muscle growth) and a decrease in irisin (a promoter of exercise-induced muscle hypertrophy) [40]. Also, an increased anabolic resistance exacerbated by an induced energy deficit was demonstrated at HA (Pikes Peak; 4300 m, 22 days), involving blunted rapamycin complex 1 (mTORC1) activity that was independent of hypoxia-inducible factor-1α [41]. Ubiquitin proteasome-mediated proteolysis was unchanged, and anabolic sensitivity to post-exercise protein (whey) ingestion was inhibited. A similar protocol, while upregulating muscle inflammation (TWEAK, TNFα-receptor, TNFα), was associated with upregulation of fibroblast growth factor-inducible 14 (Fn14) gene expression and myogenesis (myogenin) and no change in atrophic gene expression (Atrogin-1, MuRFS1) [42]. Interestingly, individuals with higher levels of Fn14 gene expression had greater upregulation of myogenin and less reduction in FFM, leading to the suggestion that an increased muscle inflammatory response to HA exposure promotes myogenesis to protect FFM during acclimatization.

Finally, the provocative suggestion has been made that a greater weight and FFM loss at HA might have the potential to improve exercise performance at HA [43]. That is, hepatic ketone bodies and muscle amino acids, released during negative energy balance at HA, could act both as metabolic substrates (preserving carbohydrate stores) and as metabolic modulators (improving mitochondrial efficiency, activating ATP-sensitive potassium channels and reducing ROS production). Indeed, ketone supplementation can improve mitochondrial metabolic efficiency, carbohydrate sparing during exercise (via suppression of anaerobic glycolysis with reduced blood lactate levels) and exercise (time-trial) performance [44].

Fatigue

It should be evident from the foregoing discussion that the determinants of $\dot{V}O_2$max and fatigue at HA and its acclimatizing profile are complex. One means to usefully quantify the expression of the fatigue process is through the power–duration relationship for high-intensity constant-WR exercise which is an inverse hyperbolic relationship between WR and its tolerable duration at SL and is characterized by the parameters CP and W′ [1].

Critical power and W′

CP is the asymptotic WR (i.e. the WR that could theoretically be sustained for an infinitely long period of time with stability of $\dot{V}O_2$ and arterial [lactate] and [H^+] [1]) and is a crucial determinant of task endurability. It can be viewed as reflecting a rate of aerobic energy-pool reconstitution that dictates the maximum WR sustainable without a progressively-increasing anaerobic contribution [45]. W′ is the area constant of the hyperbola representing a given amount of work performable > CP, regardless of WR. It has been proposed to reflect (a) an anaerobic intramuscular energy store of finite capacity (creatine phosphate, ATP), an anaerobic-glycolytic source related to lactate production and utilization of previously-stored O_2 or (b) the accumulation of fatigue-inducing substances (e.g. H^+, inorganic phosphate). And as the $\dot{V}O_2$ slow component sets to $\dot{V}O_2$ on the trajectory to $\dot{V}O_2$max [1], it is a functional index of the peripheral fatigue process(es).

The power–duration relationship has been shown to retain its hyperbolic form at HA (Ev-K2-CNR Pyramid Laboratory, Lobuche; 5050 m), but with a lower CP consistent with reduced O_2 availability and a lower W′ that was ascribed (in part) to reduced muscle-venous O_2 storage and near-limiting levels dyspnoea [7] (see Section ‘Ventilation and dyspnoea’). As a result, a given supra-CP at HA is less sustainable than at SL. Whether CP, W′ and the $\dot{V}O_2$ slow component (a) evidence any recovery expressible in an amelioration of exercise intolerance with acclimatisation or (b) are more optimal in highlanders is unknown. Also not accommodated in this schema to date are influences related to central fatigue, widely accepted to be exacerbated in hypoxia [46].

Peripheral fatigue

Constant-WR cycling (~50% of SL WRpeak) has been reported to elicit similar degrees of peripheral fatigue (i.e. downstream of the neuromuscular junction, expressed as % decrease in electrically evoked potentiated quadriceps twitch force post-exercise to pre-exercise) in lowlanders at HA (Mt Chacaltaya, 5260 m; 7–14 days) and for matched acute normobaric hypoxia, with none for SL [47]. That the duration of hypoxic exposure did not attenuate the degree of peripheral fatigue runs counter to a likely higher convective muscle O_2 delivery at HA than for acute hypoxia. It was proposed that this potential benefit was offset by a decreased capillary muscle O_2 conductance (see Section 'Muscle blood flow'). However, Sherpa at HA (Ev-K2-CNR Pyramid Laboratory, Lobuche, 5050 m; 7–14 days) demonstrated less quadriceps force loss during fatiguing exercise (intermittent electrically-evoked quadriceps contractions) and faster post-exercise force recovery than lowlanders, despite similar degrees of muscle O_2 delivery and oxygenation (ultrasonography; NIRS) [48]. It was suggested that this might reflect factors such as increased mitochondrial coupling efficiency and greater oxidative stress protection in Sherpa which, in turn, may contribute to their higher performance capabilities at HA [35••,49] (see Section 'Mitochrondrial density').

Central fatigue

In contrast to peripheral fatigue, lowlanders at HA (Mt Chacaltaya, 5260 m; 7–14 days) demonstrated a less-marked degree of quadriceps central fatigue (expressed as the exercise-induced % decrease in voluntary muscle activation) for constant-WR cycling (~50% of SL WRpeak), compared to acute normobaric hypoxia; none being evident for SL [47] (see Section 'Peripheral fatigue'). This was ascribed in part to improved cerebral tissue oxygenation at HA (transcranial Doppler; NIRS), relative to acute hypoxia.

The duration of hypoxic exposure was found to influence locomotor motoneurone excitability and the time course of supraspinal fatigue during fatiguing isometric exercise (intermittent elbow flexion, 25% maximal voluntary contraction (MVC) torque) [48] in lowlanders. Thus, muscle performance (pre-to-post exercise difference in MVC torque) was compromised with acute normobaric hypoxia with a heighted rating of perceived exertion (RPE), but recovered to SL values with HA exposure (Ev-K2-CNR Pyramid Laboratory, Lobuche, 5050 m; 7–14 days). Also, supraspinal fatigue (measured as cortical voluntary activation (cVA) using TMS) developed later at HA compared to acute hypoxia. Motoneurone excitability (measured via subcortical (cervicomedullary) stimulation during the silent period after transcranial magnetic stimulation (TMS) when cortical voluntary drive is transiently interrupted) was lower post-exercise for acute hypoxia (tentatively ascribed to a reduced cerebral $\dot{Q}O_2$), but was actually enhanced for HA. It was concluded that supraspinal and motoneurone-excitability adaptations represent components of HA acclimatization contributing to restoration of muscle performance.

A follow-up study with essentially the same design indicated that while baseline MVC torque and cVA were lower in Sherpa than lowlanders (reflective of smaller stature and body mass in Sherpa for the former, and possibly a lack of familiarization in Sherpa for the latter), neither MVC torque loss nor development of supraspinal fatigue with fatiguing exercise were different although RPE was higher for lowlanders [50••]. However, for lowlanders, corticospinal excitability (motor-evoked potential via motor cortex TMS) increased to a greater extent, peripheral excitability (maximal compound muscle action potential via brachial plexus stimulation) decreased and cerebral oxygenation (NIRS) increased more across exercise. This latter observation was tentatively suggested to reflect that Sherpa may have completed the exercise with lower sympathetic drive and motor-unit recruitment that would therefore require a lower cerebral O_2 delivery. The adaptive implications of these findings for large muscle-mass exercise require investigation.

Lactate threshold

One feature common to a large proportion of HA investigations of exercise intolerance relates to the confounding issue of defining intensity solely in terms of % $\dot{V}O_2$max or %WRmax; no account therefore being taken of the relative location of CP and θ_L within the $\dot{V}O_2$ scope at HA [1]. Robust estimation of θ_L at HA is therefore paramount. In contrast to SL, while the V-slope criterion (demonstration of the onset supplemental CO_2 output ($\dot{V}CO_2$) as a breakpoint on the $\dot{V}CO_2$–$\dot{V}O_2$ relationship for rapid-incremental exercise) consistently matched the directly-measured θ_L in a small cohort study at HA (EBC; 5300 m), the additional requirement to demonstrate hyperventilation relative to O_2 (increasing O_2 ventilatory equivalent and end-tidal PO_2) but not CO_2 (no increased CO_2 ventilatory equivalent, no decreased end-tidal PCO_2) [51] failed to correspond with the V-slope estimate in 50% of subjects [DZH Levett, PhD thesis, University College London, 2014]. This may reflect an amplification of $\dot{V}$ E by hypoxemic carotid-chemoreceptor sensitisation at relatively low WRs, that is $<\theta_L$; the consequent hyperventilation, not being specific to O_2, therefore causing hyperventilation also relative to CO_2. It was tentatively recommended that the V-slope criterion for $<\theta_L$ estimation at HA is more accurate on its own than when anchored to SL-validated supplementary gas-exchange indices.

These findings were extended to considerations of the proportional contribution of sub-$<\theta_L$ WRs to the tolerable $\dot{V}O_2$ scope at HA. Thus, it was demonstrated that θ_L in lowlanders was a progressively increasing fraction of $\dot{V}O_2$peak with increasing altitude as high as 8000 m (Mt Everest): 54.6% at SL, 57.6% at 5300 m, 58.6% at 6400 m and 65.5% at 7950 m [DZH Levett, PhD thesis, University College London, 2014]. This suggests that the relative preservation of θ_L confers a degree of protection on the moderate-intensity range of sustainable WRs at HA, although the causes(s) can only be speculated on. Furthermore, the individual variability in the HA-related θ_L decrement may explain some of the variability in exercise performance that has been described at these altitudes.

Work efficiency and economy

Whether improved mitochondrial coupling at HA is reflected in increased whole-body exercise efficiency remains controversial [38], not the least because of confounding factors such as not constraining WRs to be $<\theta_L$ (the O_2 cost of supra-θ_L WRs being increased [1]) or not allowing sufficient time for acquisition of $\dot{V}O_2$ and $\dot{V}CO_2$ steady states. Furthermore the increased oxygen cost of the work of breathing may confound and increased exercising-muscle efficiency. With these constraints in mind, delta efficiency, calculated as the percentage slope of the relationship between caloric equivalent of external work performed and gross caloric output, including resting metabolism, was unaffected by altitude: 26.9% at SL, 26.4% at 3500 m and 26.3% at 5300 m [DZH Levett, PhD thesis, University College London, 2014]; sub-θ_L exercise economy ($\dot{V}O_2$/WR), which does not take account of differences in substrate oxidation, was also unaffected. This suggests that the potentially-beneficial effects of improved mitochondrial efficiency at HA (see Section 'Muscle energetics') are either not sufficient to be expressed at the whole-body level and/or some offsetting influence is operating in tandem.

Conclusion

The etiology of exercise intolerance at HA, defined by a reduced maximal or peak $\dot{V}O_2$, is multifactorial in lowlanders and highlanders and the sites of physiological-system limitation may differ between the two groups. Sarcopenia, decreased mitochondrial density and changes in mitochondrial energetics are now recognised as important contributors alongside impaired O_2 delivery along the convective-diffusive cascade between lungs and exercising-muscle mitochondria.

Limiting factors may include exertional dyspnea, pulmonary gas exchange, cardiac (stroke volume) limitation, microcirculatory blood flow reduction and central fatigue. In contrast, it is less clear whether peripheral fatigue, overall muscle blood flow and muscle blood flow distribution are important contributors to limitation. Important differences are noted between the determinants of exercise intolerance at HA in native highlanders when compared with lowlanders. For example, Sherpas exhibit an unexpected inverse relationship between [Hb] and $\dot{V}O_2$peak along with preserved microcirculatory blood flow, enhanced efficiency of O_2 utilization, improved muscle energetics and protection against oxidative stress. Categorisation of exercise intensity based on physiological demarcators, including lactate threshold, critical power and W′, may facilitate further elucidation of exercise intolerance at altitude, and will need to take account of the altitude-dependence of these variables.

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Conflict of interest statement

Nothing declared.

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Papers of particular interest, published within the period of review, have been highlighted as:

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