The Ergogenics of Hypoxia Training in Athletes

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Hypoxia elicits hematopoiesis, which ultimately improves oxygen transport to peripheral tissues. In part because of this, altitude training has been used in the conditioning of elite endurance athletes for decades, despite equivocal evidence that such training benefits subsequent sea level performance. Recently, traditional live high-train high athletic conditioning has been implicated in a number of deleterious effects on training intensity, cardiac output, muscle composition, and fluid and metabolite balance—effects that largely offset hematopoietic benefits during sea level performance. Modified live high-train low conditioning regimens appear to capture the beneficial hematopoietic effects of hypoxic training while avoiding many of the deleterious effects of training at altitude. Because of the logistical and financial barriers to living high and training low, various methods to simulate hypoxia have been developed and studied. The data from these studies suggest a threshold requirement for hypoxic exposure to meaningfully augment hematopoiesis, and presumably improve athletic performance.

Introduction

There is little debate that training at altitude improves athletic performance at altitude [1]. For decades, elite athletes have invested considerable resources in training at altitude, with the intention of improving performance at sea level. Studies indicate that there are numerous physiologic changes associated with hypoxic and hypobaric training—some advantageous and some detrimental to athletic performance at or near sea level. Recent advances have allowed athletes to optimize the beneficial effects of hypoxic/hypobaric training while minimizing deleterious effects. Training modalities such as live high-train low (LHTL), intermittent hypoxic exposure (IHE), hypoxic/hypobaric chambers, and exercise hypoxia have changed the face of state of the art training.

This review, although by no means comprehensive, looks at the effects of hypoxic/hypobaric training from a performance enhancement and systems-based perspective. Training recommendations are made, and future research is suggested.

Performance-based Responses to Altitude

Altitude training has been incorporated into endurance athletes' preparation for decades. At first, athletes employed a traditional live high-train high (LHTH) exercise program. Research failed to show that this improves aerobic performance at sea level, although anaerobic performance may be enhanced [2–4]. More recently, modified altitude training regimens (ie, LHTL) have been shown in some well-designed studies to improve subsequent endurance performance at sea level [5,6,7•,8,9]. Because altitude training, especially LHTL, is logistically difficult as well as financially restrictive for many athletes, newer hypoxic training modalities have been developed, including intermittent hypoxic exposure, hypoxic tents, and hypoxic exercise. Studies of such simulated altitude exposure have produced mixed results with regard to performance [10•].

Altitude training appears to benefit elite athletes principally through an improvement in oxygen transportation. This is achieved largely by an increase in hematocrit and blood volume [11,12], although a concomitant volume contraction and decrements in cardiac output in short-term altitude exposure may mitigate these benefits [13,14]. Other deleterious effects of exercise at altitude include a relative detraining effect, which can offset any improvements in oxygen-carrying capacity [15,16].

Optimal endurance performance relies upon frequency, duration, and intensity of training [17,18]. Especially with endurance performance [19], maintenance of training intensity appears to be the principle variable in optimizing subsequent endurance performance [20,21]. Failure to maintain training intensity results in lower VO_2max [20–24], and a subsequent detraining effect [15,16]. The reasons for the detraining effect appear to be multifactorial. Oxygen uptake at a main-

tained power output at sea level and altitude is similar [6,25–27]. Because VO_2max declines with increasing altitude (a function of decreased atmospheric oxygen content), a given power output at altitude will correspond with a greater relative exercise intensity (higher % VO_2max). At the same absolute intensity, exercising at altitude results in higher blood lactate, heart rate, ventilation, and perceived effort compared with similar training at sea level [13,28]. Athletes training at altitude therefore self-select reduced work rates [5,6]. Thus, training power output is typically reduced at altitude compared with sea level for any given amount of work done [5,29], with subsequent relative deconditioning in altitude training versus sea-level training [15,16].

LHTL programs and simulated intermittent hypoxia/hypobaria training regimens have been designed to capture the beneficial hematopoietic effects of altitude exposure, while avoiding the detraining effects of altitude. Results of several well-designed studies involving LHTL have proven benefits to subsequent sea-level performance in endurance athletes [6,30••]. The performance enhancement during these LHTL studies can be impressive. For example, over a 27-day training period, elite runners showed a 1.1% improvement in 3000 meter time trial time in spite of their recent participation in a national championship competition [30••]. One third of the athletes achieved a personal best time subsequent to the LHTL training protocol. Results were similar among both male and female participants.

IHE can avoid the intrinsic logistical and financial constraints of LHTL. Some studies of IHE have also investigated the threshold hypoxic stimulus required to effect performance enhancement. Initial uncontrolled studies of IHE reported significant improvements in anaerobic threshold, hematologic measures, and ventilatory measures after 17 days of 3 to 5 hours per day of altitude exposure at 4000 to 5500 meters [31]. The same research group had previously demonstrated no difference in performance benefit whether the hypoxia was administered at rest or during exercise [32].

Evidence for performance enhancement in simulated hypoxic environments can be extrapolated from data regarding hematopoiesis. Some studies have found no erythropoietic effect with normobaric hypoxia during sleep [33–35], although hypoxic exposures were for less than 10 hours per day for less than 3 weeks. Other researchers have found an increase in erythrocyte mass with exposures of 16 hours per night for 4 weeks [36,37]. Studies of 12 hours per day of hypoxia during rest at a simulated altitude of 2000 to 2700 meters failed to show an improvement in VO_2, although erythropoietin and reticulocyte counts were improved [38]. Significant improvement in 3000-meter timed trial after 3 hours per day of hypoxia for 14 days was reported [39]. A more recent study of 70 minutes a day of alternate 5-minute cycles of hypoxia and normoxia 5 days a week for 4 weeks did not show improvement in hematologic or performance measures [40]. These studies together suggest a threshold dose of hypoxia required for augmented hematopoiesis [10•]. The details regarding the degree and duration of hypoxia required for athletic enhancement remain to be elucidated.

Putative Mechanisms of Physiologic Adaptation During Altitude Training

Hematologic

Altitude exposure augments the hematopoietic response. This has been postulated as one of the key benefits of altitude training; transfusion studies and recombinant erythropoietin studies suggest that increased erythrocyte mass alone increases VO_2max for endurance athletes regardless of performance level [41–45]. There are also deleterious hematologic effects associated with brief altitude exposure, including volume contraction and subsequent perfusion decrements. Training modalities such as LHTL may maximize the erythropoietic effects of altitude training while concomitantly reducing deleterious hemodynamic effects.

Natives living above 2500 meters demonstrate a significantly higher hemoglobin, hematocrit, and erythrocyte volume compared with sea level residents [12,46]. The polycythemia of altitude residence seems to depend on the duration of habitation at altitude [47,48]. Studies suggest a threshold altitude of 2200 to 2500 meters, corresponding to a threshold PO_2 of 70 mm, is needed for altitude-dependent hematopoiesis [12]. The hematopoietic response is greater at higher altitudes, likely secondary to increasing hypoxia and subsequent release of higher levels of erythropoietic factors at higher altitude [12].

Hematopoiesis increases continually during altitude training. Berglund [48] found that hemoglobin concentration during acute altitude training increased at approximately 1% per week. The apparent benefit to athletes of increased hemoglobin concentration may be offset by concomitant sympathetically mediated arterioconstriction and decreased cardiac output, which combine to prevent an increase in O_2 transport overall for those undergoing traditional altitude training [14]. In addition to those cardiovascular effects, athletes during an altitude sojourn may lose up to 25% of their plasma volume [13], although athletes who reside at altitude appear to maintain plasma volumes comparable with athletes residing at sea level [49]. Such hemodynamic changes may contribute to a decrement in muscle perfusion at altitude which persists upon return to sea level [14].

LHTL has been shown to increase markers of hematopoiesis, erythrocyte volume, and hemoglobin concentration in competitive and elite athletes [6,30••]. These findings have been correlated with increased VO_2max and performance measures [6,30••].

The results of studies of simulated altitude exposure have been mixed with regard to hematopoietic effects.

Twenty-three nights of 8 to 10 hours at a simulated altitude of 3000 meters in a nitrogen house did not elicit a change in total hemoglobin mass or hematopoietic markers compared with control subjects [33]. A 4-week regimen of alternating 5-minute cycles of hypoxia and normoxia for 70 minutes five times a week did not alter erythropoietic markers in highly trained runners versus control subjects [40]. Among well-trained runners, an 8- to 11-hour per night exposure to a simulated altitude of 2650 meters for 5 nights, followed by a 3-night sojourn, and then repeated for three cycles, resulted in an increase in serum erythropoietin but did not increase reticulocyte production versus control [35]. These findings are consistent with the suggestion that there are minimum requirements for the degree and duration of hypoxia required for effective erythropoiesis.

Respiratory

Altitude training has both positive and negative effects on the respiratory conditioning of athletes. Training at altitude may result in improved respiratory muscle training because of an increase in resting and exercise ventilation [50]. This increase in ventilatory exchange (VE) at altitude is well documented [51–53], and has been associated with increased respiratory muscle work at altitude, which persists upon return to sea level [52]. The primary mechanism of increased VE at altitude is augmentation of the hypoxic ventilatory response (HVR), which has been found during continuous altitude residence [54], intermittent hypoxic exposure [55], and LHTL [56•,57]. The increased HVR facilitates a progressive rise in VE despite unchanged hypoxic stimulus and hypercapnic inhibition [51]. On return to normoxia, this hyperventilation continues and then diminishes in a time-dependent manner [51].

The physiologic effects of this increased ventilatory exchange during exercise are unclear. Hyperpnea during exercise may be detrimental because of reduced peripheral blood flow to compensate for the greater blood flow demands of breathing [58]. Conversely, insufficient exercise hyperpnea may lead to exercise-induced hypoxemia at submaximal workloads [59,60], although it is unclear whether this affects performance.

Traditional altitude training has been found to augment HVR and VE after 2 to 4 weeks [61–64]. The duration and degree of hypoxia required to augment HVR and VE in subsequent sea level performance using an LHTL protocol or simulated altitude exposure is unclear. As little as 1 hour a day of hypoxia for 7 days was enough to increase HVR, although submaximal VE remained unchanged [65]. Another study found that 45 minutes a day of 2500-meter hypoxia, 5 days a week for 5 weeks during exercise increased HVR but not VE [5]. Subjects exposed to hypoxia for 8 to 10 hours a night at 3000 meters showed increased submaximal exercise VE in normoxia after 11 days, although HVR was not measured [57]. Other research has found a 37% increase in ventilation during cycling at fixed velocity after 8 days of LHTL [66].

A more recent controlled study found that exposure to 4 nights of LHTL increased submaximal exercise VE measured in normoxia by 9%, and remained elevated throughout a 3-week intervention [67]. This increased VE was strongly correlated with an increased HVR by 15 to 19 days of LHTL, with a maximal HVR at 19 days of training—effects that were not noted in sea level control subjects [67]. This is the first study to report increased submaximal VE in normoxia after 4 days of LHTL in well-trained athletes [67].

No increased VO_2max was noted after 19 days of LHTL [67]. This finding is in accord with most previous studies of traditional altitude training and LHTL alike, which raises the question whether increased submaximal but not maximal VE is a reflection that trained athletes may be limited by mechanical constraints of the pulmonary system at high workloads [68]. It has been suggested that expiratory flow limitation during maximal exercise limits VO_2max [69,70].

VO_2max during acute altitude exposure in athletes is diminished, even at altitudes as low as 580 meters [71] and 900 meters [72]. The decrement in VO_2max in hypoxia is directly proportional to VO_2max in normoxia, suggesting that athletes are affected more negatively by altitude exposure than untrained subjects. It is unclear whether observed decrements in VO_2max affect performance, as significant improvement in exercise performance without improved VO_2max has been demonstrated [1,18,63,73–75]. Furthermore, improvements in VO_2max may not necessarily evoke improvement in exercise performance [6].

Cardiovascular

The effects of traditional altitude training on the cardiovascular system appear to be largely deleterious to sea level performance. Although chronic exposure to hypobaric hypoxia increases arterial oxygen concentration as a result of an increased hemoglobin concentration, sympathetically mediated arterioconstriction and decreased cardiac output prevent an increase in oxygen transport [14]. The proposed mechanism for the reduction in cardiac output observed at altitude is decreased vegetative stimulation [13], possibly by downregulation of β-adrenoceptors [76]. This may lead to a negative altitude training effect on the heart. It is unclear whether modified altitude training regimens, such as LHTL and IHE, avoid the cardiac detraining associated with chronic altitude exposure.

Musculoskeletal

The effects of prolonged altitude exposure on muscle structure and function appear to be largely deleterious. Prolonged exposure to altitudes above 4500 meters has been shown to result in reduced muscle mass [77]. Muscle perfusion is decreased at altitude, and that perfusion deficit persists after return to sea level [14,78]. Above 4300 meters, altitude exposure is associated with loss of mitochondria and oxidative enzyme capacity [79]. Simi-

Table 1. Quality of evidence: ergogenics of hypoxia training

Study	Study findings	Strength of evidence
Martino et al. [3], Nummela et al. [4], Levine and Stray-Gundersen [6], Levine et al. [7•], Levine et al. [8], Levine et al. [9], Stray-Gundersen et al. [30••]	Live high-train low improves athletic performance	Level 1
Katayama et al. [39]	Simulated hypoxic exposure improves athletic performance	Level 2
None listed	Live high-train high improves sea level athletic performance	Level 3
Boutellier et al. [14], Gore et al. [71]	Live high-train low harms sea level athletic performance	Level 2

Table 2. Assessing quality of evidence

Study quality	Diagnosis	Treatment, prevention, screening, outcomes	Prognosis
Level 1: good quality patient oriented evidence	Validated clinical decision rule	SR/meta-analyses or randomized controlled trials with consistent findings	SR/meta-analysis of good-quality cohort study
	SR/meta-analyses of high-quality studies	High-quality individual randomized controlled trials	Prospective cohort study with good follow-up
	High-quality diagnostic cohort study	All or none study	
Level 2: limited quality patient-oriented evidence	Unvalidated clinical decision rule	SR/Meta-analysis of lower-quality clinical trials or of studies with inconsistent findings	SR/Meta-analysis of lower quality cohort studies or with inconsistent results
	SR/meta-analysis of lower-quality studies or studies with inconsistent findings	Lower quality clinical trial	Retrospective cohort study or prospective cohort study with poor follow-up
	Lower quality diagnostic cohort study or diagnostic case-control study	Cohort study	Case-control study
		Case-control study	Case series
Level 3: other evidence	Consensus guidelines, extrapolations from bench research, usual practice, opinion, disease-oriented evidence (intermediate or physiologic outcomes only), or case series for studies of diagnosis, treatment, prevention, or screening.		

SR—systematic review
(*Adapted from* Ebell et al. *Am Fam Physician* 2004, 69:549–557.)

lar results have been documented after altitude training at 2700 meters, and low-pressure chamber training with equal relative intensity [2,80,81]. Athletes exposed to an equal absolute workload showed increased oxidative capacity and myoglobin concentration on return to normoxia [79,81–83]. Other studies indicate that anaerobic metabolic enzymes are not enduringly affected by altitude exposure [84]. The effects of hypoxia on muscle capillary networks is unclear [2,80,81,85]. Only Mizuno et al. [2] and Hoppeler and Vogt [86] documented increased muscle capillarity after altitude exposure, possibly due to a confounding effect of improved conditioning in muscles not fully trained previously.

Chronic altitude residence has previously been found to augment muscle oxidative capacity [87]. Muscle biopsies have shown higher myoglobin and oxidative enzyme

concentrations in high altitude natives compared with sea level counterparts [87]. These initial findings may simply be due to differences in training level between altitude and sea level subjects [88,89].

Conclusions

Training at altitude improves performance at altitude. Increasingly, data suggest that traditional LHTH conditioning is deleterious to subsequent sea level performance. Intermittent hypoxic exposure, as best exemplified by several studies of LHTL training regimens, has been shown to improve sea level performance. Simulated hypoxic exposure, although promising, has shown mixed results. The lack of a consistent improvement in performance or markers of hematopoiesis during studies of simulated hypoxic exposure is likely secondary to the great variability in duration of hypoxic exposure among such studies. These studies suggest a threshold degree/duration of hypoxia required for significant hematopoiesis and subsequent performance enhancement. As little as 3 hours of hypoxia a day for 2 weeks has been linked to improvement in subsequent timed trial performance [39]. Other studies of IHE with various training parameters have shown improved hematologic measures [36–38], although others have shown no such improvement [33–35].

Based on a review of current literature, only LHTL conditioning has been shown to improve performance in well-controlled prospective studies. There is no evidence that hypoxia during training benefits performance. In fact, studies of traditional altitude training suggest that training in hypoxia has the negative effect of reduced training intensity. Simulated hypoxic exposure studies are promising, but have yet to be proven to augment athletic performance definitively (Tables 1 and 2).

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