CLINICAL REVIEW

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Hypoxic Training in Natural and Artificial Altitude

Hypoxietraining in natürlicher und künstlicher Höhe

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Summary

› **Many endurance athletes** aim to increase endurance performance at or near sea-level by hypoxic training, which can be realized in natural or artificial altitude via three main concepts: living and training in hypoxia, living in hypoxia and training in normoxia, or living in normoxia and training in hypoxia.

› **The scientific evidence for these concepts** is surprisingly unclear, although several ergogenic adaptations to hypoxic training are well described. Hematologic acclimatization through an increase in hemoglobin mass is often considered the most important factor. But hematologic acclimatization does not explain the performance increase found by some studies, indicating other mechanisms and confounders determine successful training adaptation.

› **This clinical review briefly summarizes** the current, conflicting knowledge, lists confounders potentially influencing the outcome, and provides some practical guidance to coaches and clinicians for monitoring and optimizing hypoxic training as far as covered by evidence.

KEY WORDS:
Hypoxia, Endurance Performance, Wearables, Elite Athletes, Endurance Training, Hemoglobin, Erythropoiesis

Introduction

Beginning with the 1968 Olympic Games in Mexico, hypoxia training has become a regularly used method by elite endurance athletes and numerous national athletic programs to prepare for altitude or (near) sea-level competitions (2, 22, 37). This clinical review focuses on the aim of improving sea-level performance through hypoxic training at natural or simulated moderate altitude in highly trained and elite endurance athletes. There is a considerable and growing body of scientific literature on this topic, but the evidence is by no means conclusive [e.g., (19,34)]. Here, we aim to summarize the existing knowledge of altitude training for increasing sea-level performance, to highlight the ambiguities, and to outline guiding principles within the narrow corridors of evidence.

Hypoxia

Hypoxia is a deficiency of oxygen on the tissue level. In healthy humans, hypoxia can occur during severe intensity exercise, but typically it is due to a lack of oxygen in inspired air. This may be due to "natural" altitude, where barometric pressure is lower and thus partial pressure for oxygen is reduced (i.e., hypobaric hypoxia). At natural altitude, other environmental factors also change, i.e., lower air temperature, humidity, and density, but higher radiation and ozone exposure. "Artificial" altitude is most commonly induced by lower oxygen concentration in an otherwise unchanged environment at ambient air pressure (i.e., normobaric hypoxia). Acclimatization to natural and artificial hypoxia is generally very similar (29) and thus training adaptations are similar, despite differences in e.g., ventilatory response, fluid balance, or risk of acute altitude illness (20).

Hypoxia causes a decrease of maximum oxygen uptake ($\dot{V}O_2max$) that amounts to roughly 6.0-7.5%/1000 m altitude in not acclimatized endurance athletes and is detectable from 300-800 m onwards (5, 45). As a consequence, time trial performance (i.e., exercise lasting more than 2 min) decreases by approximately 6.5–7%/1000 m after acute exposure (5, 6). Humans can acclimatize to hypoxia to a certain extent, but even at 2300 m altitude this is incomplete, so that performance remains ~6% below that at sea level even after 3 weeks of altitude

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acclimatization (33). Despite the detrimental effects of hypoxia on performance, certain aspects of altitude acclimatization may have the potential to improve performance in normoxia.

General and Performance-Related Aspects of Acclimatization to Hypoxia

Individual responses to hypoxia occur after only a few seconds and extend over minutes, weeks, and even years, depending on the degree of hypoxia and continuity of exposure. In order to optimize training programming and to effectively use altitude training within a long-term periodized approach, it is important to consider the temporal dynamics of the acclimatization illustrated in Figure 1.

The most obvious and nearly immediate response to hypoxia is hyperventilation, which is an essential and very effective compensatory mechanism directly improving arterial O_2-content, causing a higher ventilation at a given power output. Hyperventilation does not only increase alveolar PO_2, but also induces a respiratory alkalosis due to the reduction of alveolar and arterial PCO_2, imposing a transient left shift of the oxygen dissociation curve. In moderate altitudes, alkalosis is renally compensated within 24 h, but the price to pay is a decreased buffer capacity due to the loss of hydrogen bicarbonate. However, at moderate altitude a rightward shift of the oxygen-dissociation curve is observed due to the higher concentration of 2.3-BPG. Particularly during exercise, this right shift facilitates dissociation of oxygen from hemoglobin to the tissue counteracting the impaired alveolar oxygen extraction (17). It is also worth mentioning that the young erythrocytes who also have beneficial rheological properties and higher 2.3-BPG concentration are not hemolyzed after return to sea level (14).

A substantial increase of resting and sub-maximum heart rate is another, very rapid response that augments cardiac output and thus helps to maintain the oxygen supply to the tissue. This response is mediated by a hypoxia-induced shift of the autonomic nervous system towards sympathetic dominance, which is a systemic reaction. Recent data from 3450 m indicate that this reaction may be attenuated in highly endurance-trained athletes, leading to an impaired acclimatization on the first day that has to be considered in training planning (28). Of note, both heart rate and ventilation are significantly altered so that these two variables are no longer linked to exercise intensity as they are at sea level.

A more delayed response is a plasma volume shrinkage of ~6% after one day. Due to this loss of volume, hemoglobin concentration increases by approximately 0.6 g/dL at 2500 m (1), causing a higher amount of oxygen carriers per unit of blood, but notably not to an increase in absolute oxygen transport capacity. In turn, the lower blood volume decreases cardiac preload and thus sub-maximum and maximum cardiac stroke volume, to which also the shortened diastolic filling time due to the increased heart rate contributes. Both have a negative effect on cardiac output and consequently on $\dot{V}O_2$max (35).

But these early reactions cannot fully compensate for the PO_2 decrease in tissues, mediating a stabilization of hypoxia-inducible factors (HIF 1α, 2α). As a result, transcription and translation of the erythropoietin (EPO) gene are stimulated and within 2 h an increase in serum [EPO] is observed, peaking after 2-3 days at altitude. [EPO] may decrease to baseline in the following days and weeks of hypoxic exposure (eg., (44)), but magnitude and time course seem to depend on the degree of hypoxia. EPO initiates erythropoiesis and an increasing number of reticulocytes can be detected in the blood after 3-5 days,

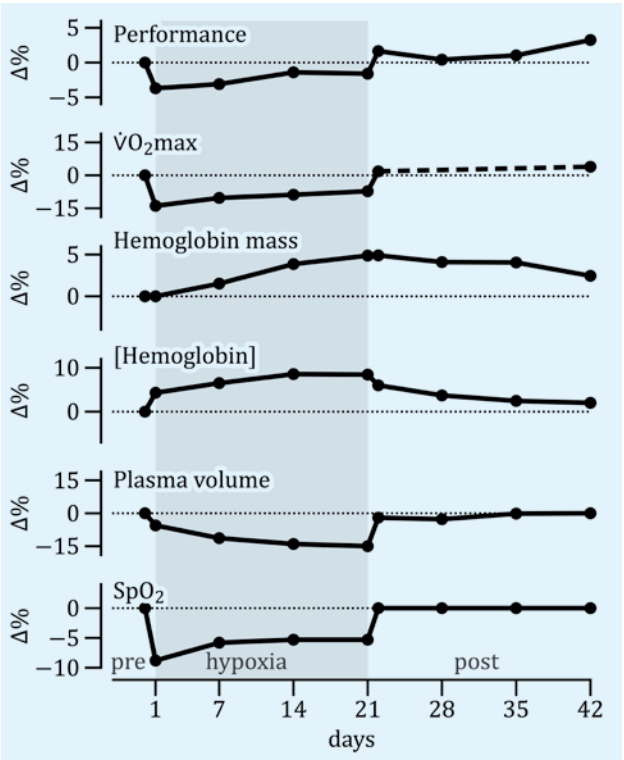

Figure 1

Average time course of performance and adaptation during and following 3 weeks of hypoxic training. Data represent approximates based on the literature. Please see supplemental material, online only. [Hb]=hemoglobin concentration; Hbmass=hemoglobin mass; SpO_2=peripheral oxygen saturation; performance=running or swimming speed.

imposing an absolute increase in hemoglobin mass (Hbmass) of ~2% after 10 days at 2300 m (44). A substantial ~4-5% increase can be expected after 3 weeks and studies lasting 4 weeks did not observe a leveling off at 2300 m (27). The increase in Hbmass is a true increase in oxygen transport capacity of the blood. It is probably the most prominent aspect of acclimatization expected to improve performance at sea level, since a change of 1 g hemoglobin mass is associated with an increase in $\dot{V}O_2$max of approximately 4 mL/min (32). The Hbmass increase is very heterogeneous and data reported range from no response to 12% (44). Figure 2 mirrors potential and proven confounders contributing to this variability.

Aside from these effects, responses to training in hypoxia have been reported in a variety of skeletal muscle cell types and other tissues by measuring mRNA level (43), which must not be interpreted in isolation. Several aspects of acclimatization are related to the hypoxia mediated HIF-stabilization that does not only increase [EPO], but also impacts vascular endothelial growth factor, glycolytic enzymes, monocarboxylate transporter 1 and 4, and other variables that influence metabolism and thereby performance (see (11) for review and references). Receptors for EPO itself are to be found on a variety of tissues, suggesting an influence of EPO on angiogenesis and possibly indicating a cardioprotective function (see (46) for review)

Hypoxia Training Concepts

Traditionally, athletes traveled to altitude to sleep and train. But for the last 30 years other concepts have been developed that can also be combined with each other (Figure 3). ›

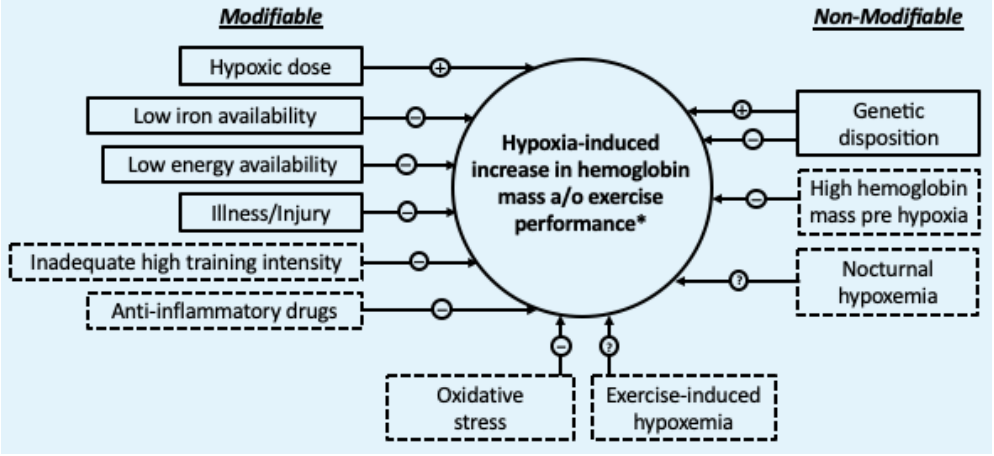

Figure 2

Proven and possible determinants of hypoxic training induced increase in hemoglobin mass and/or exercise performance. Boxes with dashed outline indicate conflicting and / or (a/o) unclear scientific evidence; * indicates that gain in exercise performance following hypoxia training is also attributable to other mechanisms than increased Hbmass; + and – indicates unclear association.

Live High – Train High (LH-TH)

The traditional LH-TH camps are designed especially for endurance athletes. Here, athletes sleep and train at altitude. Camps usually last 2-3 weeks and are sometimes held for two to three times per season. Optimum altitude for increasing hemoglobin mass is probably 1800–2500 m. Due to hypoxia, performance capacity decreases, necessitating a reduction of external training load.

Live High – Train Low (LH-TL)

Finnish and American scientists created the LH-TL concept in the early 1990s to circumvent the reduction in external training load and potential loss of strength. In LH-TL, athletes live and/or sleep either at natural or artificial altitude and train in normoxic (i.e., near sea-level) conditions. Due to logistical difficulties of realizing LH-TL in the mountains (travel time etc.), artificial altitude is generally preferred. But the opposite way been has also reported, i.e., to live in natural altitude and then to train in approximated normoxia by supplementing oxygen (47). To induce effective erythropoiesis, exposure to hypoxia should last ≥14 h/day for 2-3 weeks at natural or simulated altitude ≥2100 m (31).

Evidence of Increase in Endurance Performance after Living High Camps

In elite athletes, performance increases of 5.2% after LH-TH (~2400 m) and 4.3% after LH-TL camps (~2900 m) were calculated, clearly indicating that such training concepts can be successful. However, these results are based on a limited selection of studies (2). Due to the high individual variability, numerous methodologically limited studies, and contradictory results even within the few high-quality studies, we do not see reliable evidence for performance improvements after LH-TH or LH-TL.

Nevertheless, considerable performance improvements have also been reported for combined concepts, called LH-THTL. Here, athletes live and sleep in hypoxia (LH) and they conduct low- and moderate-intensity training in hypoxia (TH), which contributes the largest proportion of an endurance athlete's schedule. Of note, they generally perform high-intensity training sessions in normoxia (TL) to circumvent reductions in external load (27).

To explain the ambiguity in the data, it is worth mentioning that timing of testing and/or competing are crucial for the outcome, but exact data are scarce. According to our experience, few athletes demonstrate a first peak in performance 1-3 days after return to normoxia, followed by a 2-week low in performance, which is similar to data of (21). Maximum performance is usually achieved after approximately 3 weeks, which is in line with scientific data on swimmers, for both competition and standardized testing. However, at that time point, ~50% of the Hbmass increase is already lost on the time course, underlining that the gain in performance is only partially attributable to hematological acclimatization (44).

Live Low – Train High (LL-TH)

With live low–train high (LL-TH), athletes train in hypoxia, while spending the remaining time in normoxia. This concept has gained enormous popularity in recent years. It is applied for medical purposes such as improving rehabilitation intervention outcomes (24) and by athletes, e.g., from team sports, who can hardly participate in live high-training camps for practical reasons, like e.g., their tournament schedule. At least three different LL-TH protocols are applied (for review see (10)).

1. Continuous hypoxic training (CHT), where athletes perform at least 20-min lasting bouts of moderate intensity exercise in order to improve low intensity endurance performance.
2. Interval training in hypoxia (IHT), where athletes conduct moderate to high intensity interval exercise lasting 0.5 – 5.0 min. The pause is similar to the duration of the preceding work interval. Aim is to improve $\dot{V}O_2$max.
3. Repetitive sprint training in hypoxia (RSH), where athletes perform short (5-30 s) high-intensity exercise with incomplete recovery times (20-180 s). Here, athletes aim to reduce fatigue of repeated sprinting, which can be particularly relevant for team sports like e.g., soccer (3).

Evidence of Increase in Exercise Performance after Living Low Camps

With none of these concepts the time in hypoxia necessitated for effective erythropoiesis is achieved, consequently erythropoietic effects have not been reported. However, acclimatization may involve other molecular changes, which do not necessarily but possibly allow for a detectable aerobic adaptation. These include increased citrate synthase activity, mitochondrial density, capillary-muscle fiber ratio, muscle fiber cross-section, increased mitochondrial biogenesis, altered carbohydrate and mitochondrial metabolism, or defense against oxidative stress and improved buffer capacity (4, 8).

Enhancements of sea-level performance following CHT or IHT and their combination with normoxic training are controversially discussed (10, 18), and there are also no convincing data for intermittent hypoxic exposure (i.e. , hypoxia without exercise) or resistance training in hypoxia.

RSH, on the other hand, is a relatively young approach that has attracted great scientific and practical interest. The majority of studies describe improved resistance to fatigue in repeated sprints (1–5%) without improvement in maximum sprint performance (3).

Aside from these endurance training-based concepts, resistance training in hypoxia (RTE) or intermittent hypoxic exposure (IHE) may provide benefits for athletes to prepare for sojourn, training, or competition at altitude, but we are not aware of any data proving ergogenic effects for sea-level performance.

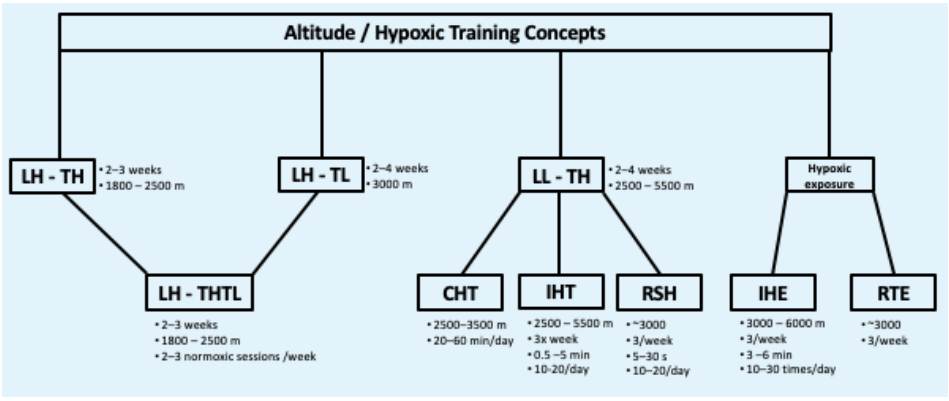

Figure 3

Overview of hypoxic training concepts (modified from (10, 21)).LH-TL=live high – train low; LH-THTL = live high – train high and low; LL-TH=live low – train high; CHT=continuous hypoxic training; IHT=interval hypoxic training; IHE=intermittent hypoxic exposure at rest; RSH=repetitive sprint training in hypoxia; RTE=resistance training in hypoxia.

Repeated Application of Hypoxic Training Camps and Periodization

Hypoxic training is not limited to a single training camp per season (e.g., before an important competition), but can be applied repeatedly throughout the season to benefit from previous acclimatization to accumulate ergogenic effects (German: "Höhenkette"). We are not aware of detailed data on the prevalence of such periodization, but we consider it to be relatively common and it is certainly applied by top athletes (37). However, data allowing us to judge its effectiveness are scarce. Saunders et al. for example reported a consecutively accumulated 10% increase in Hbmass in four swimmers within a 3-4 year period that incorporated several hypoxic exposures, but these data do neither show how muscle mass developed (which is closely correlated to Hbmass (42)), nor have training details or other confounders been reported (30). However, there is evidence that altitude acclimatization can be preserved in terms of arterial oxygenation and improved exercise capacity at 5 and 21 days after descent, though not mirrored by increased [Hb] (40). Metabolomic profiling added molecular elements to the puzzle, indicating an adenosine-dependent "erythrocyte hypoxic memory" potentially contributing to the positive effects (38, 41). Generally, it has been suggested to keep a duration of at least 8 weeks between altitude training camps to prevent excessive fatigue and to be able to periodize the training reasonably in the normoxia phases (26), but also shorter durations have been reported (37).

Confounding Factors and Practical Applications

Several confounding factors need to be acknowledged when interpreting the response to hypoxic training in scientific studies and individual athletes. To monitor, control, and optimize these factors is key for practical and successful application of hypoxic training.

Sufficient iron availability is a precondition for successful erythropoiesis. Thus, it is imperative to assess iron metabolism long term before a hypoxic training intervention and to consider appropriate supplementation. Following recent recommendations, ferritin concentrations <15 µg/L represent the threshold for considering parenteral iron supplementation due to a severe iron-deficiency restricting erythropoiesis. If ferritin is <35 µg/L, a sports physician should also be contacted to discuss immediate oral supplementation. Even with higher ferritin concentrations ranging 100-130 µg/L, oral supplementation of 100 mg/day elemental iron is recommended before and/or at least during a hypoxic camp by Australian experts (39). Other researchers, in contrast, did not report a benefit from ferritin concentrations higher than 35 µg/L pre altitude or from iron supplementation in respect to Hbmass increase in endurance athletes with clinically normal iron stores (15). However, findings remain controversial (12).

In order to maintain health and training adaptivity in normoxia, it is essential to meet the energy demand and also to avoid relative energy deficiency in sports. This is especially true in hypoxia, where resting metabolic rate increases with altitude and time at moderate altitude (48). To reduce the potentially detrimental influence of increased oxidative stress in hypoxia (13) it is actually recommended to integrate ample amounts of antioxidant-rich foods (e.g., orange juice) into athletes' daily dietary regime, but antioxidant supplements are currently not recommended as they might even impair desired effects (39).

Generally, a decrease in external training load is strongly recommended and successful coaches agree that the completion of the training volume has a higher priority than intensity [own observation]. Especially during the first days at an altitude of 3450 m, not acclimatized endurance-trained athletes are at higher risk for developing acute mountain sickness compared to untrained controls (28). This indicates pre-acclimatization and/or a substantial reduction in external load.

The overall time course of acclimatization is partly attributable to the response of the autonomic nervous system (36), which can be estimated via heart rate variability if standardized conditions are applied (28). Blood oxygen saturation is a surrogate of acclimatization that can be monitored non-invasively with oxygen pulse monitors. The rapidly advancing development of wearable technology, e.g., wrist-worn devices regularly used by endurance athletes to track their training, is promising a continuously assessment of such measures (16). Such monitoring might be especially useful to quantify the individual "hypoxic dose" (9) at rest, exercise, and during sleep, because also nocturnal blood deoxygenation has the potential to contribute to hematological and ventilatory acclimatization (23).

Another potential confounder (or determinant) is exercise induced arterial hypoxemia (EIAH), which is a persistent decrease of arterial PO_2 in a normoxic environment of at least 10 mmHg (roughly corresponding to -4% on a pulse oximeter) from rest to exercise (25). Currently it is unclear, how the degree of EIAH in normoxia is related to its magnitude occurring ›

in hypoxia, if one or the other facilitates or impairs acclimatization, as is the contribution of EIAH to the heterogeneity of the adaptation to hypoxic training (7).

Impairment of erythropoiesis and performance occurs when athletes become ill or injured during altitude training, consequently Hbmass does not increase or even decreases (15, 44). According to our experience, non-steroidal pain medication might also mitigate desired effects. Finally, it has to be noted that the heterogeneity of evidence might partly be attributable to unreported or unknown applications of EPO or blood doping methods in particular studies. Altogether we believe that these confounding factors, either individually or in combination, contributed substantially to the heterogeneous results in the literature and explain a large proportion of the so-called non-responders.

Conclusion

Despite the extensive body of literature, clear evidence and practical guidelines how hypoxic training allows for an increase in endurance performance at sea level is still lacking. What does seem clear, however, is that healthy athletes can increase their hemoglobin mass through hypoxia, and thus their oxygen transport capacity, given a sufficient hypoxic dose, energy and iron availability. However, this relatively well-controllable part of acclimatization only partially explains the performance improvement reported by some studies. Other aspects of non-hematological ergogenic acclimatization are still incompletely understood, as are the numerous confounders that can explain non-adaptation to hypoxic-training. We recommend to monitor and – if possible – manage confounders as best as possible before, during, and after a hypoxic intervention to allow for subsequent, individual optimization.

Conflict of Interest

The authors have no conflict of interest.

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