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SHORT INTERMITTENT HYPOXIA FOR IMPROVEMENT OF ATHLETIC PERFORMANCE: REALITY OR A PLACEBO?

KRATKOTRAJNA INTERMITENTNA HIPOKSIJA ZA IZBOLJŠANJE ŠPORTNE SPOSOBNOSTI: REALNOST ALI PLACEBO?

ABSTRACT

Different hypoxic training modalities have become a common addition to endurance athletes' training during the last few decades. Recently, technological advancements allowing for the simple simulation of altitude exposure by employing normobaric hypoxia have led to an even greater increase in their utilisation. It has been suggested that, besides classical hypoxic protocols employing longer exposures (> 12 h·day^{-1}), performance can also be enhanced by intermittent protocols utilising shorter daily exposures (< 6 h·day^{-1}) either at rest or combined with exercise. Even though the latest study findings regarding their influence on improved performance are ambiguous, they are habitually used in elite and recreational sport, chiefly due to their convenience and simple application. This short review will focus on currently used hypoxic training modalities with special reference to the effects of protocols utilising short exposures on performance at sea level and altitude. Moreover, the main underlying physiological mechanisms that can lead to improved performance following protocols utilising short hypoxic exposures will be reviewed. We will also examine the individual variability in response to hypoxic stimuli and possible combinations of hypoxic modalities for enhancing performance following hypoxia manipulations. The cumulative body of knowledge, as reviewed in this paper, does not indicate a robust improvement in performance as a consequence of short intermittent exposures in normobaric hypoxia. However, beneficial adaptations can be anticipated in some athletes and an individualised approach is thus warranted.

Key words: hypoxemia, acclimatisation, training models, interval hypoxia

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POVZETEK

Hipoksični trening je postal v zadnjih desetletjih eden najpogostejših dodatnih vadbenih protokolov. K še večji uporabi tovrstne vadbe je v zadnjem obdobju pripomogel tudi tehnični napredek na področju simulacije nadmorske višine, ki danes z uporabo normobarične hipoksije, omogoča enostavno simuliranje višinskih razmer. Poleg protokolov, ki uporabljajo daljše izpostavitve hipoksiji (> 12 ur·dan^{-1}), naj bi tudi protokoli s krajšim trajanjem (< 6 ur·dan^{-1}) posameznih izpostavitev hipoksiji, z istočasno vadbo ali brez nje lahko izboljšali športno sposobnost. Tovrstni kratkotrajni protokoli so v zadnjem času vedno bolj popularni tako med tekmovalnimi in rekreativnimi športniki kljub dejstvu, da trenutni rezultati raziskav ne potrjujejo jasne učinkovitosti. Pričujoči pregledni članek podaja pregled trenutno najbolj pogosto uporabljanih hipoksičnih protokolov s povdarkom na protokolih, ki slonijo na uporabi kratkotrajnih izpostavitev hipoksiji. V članku so na kratko predstavljeni tudi glavni mehanizmi, ki lahko vodijo do izboljšanja sposobnosti preko hipoksične aklimatizacije. Poleg navedenega je v članku predstavljena tudi problematika različnih individualnih odzivov na hipoksični impulz ter možnosti kombiniranja različnih hipoksičnih protokolov z namenom čim boljšega skupnega učinka hipoksične manipulacije. Rezultati pregleda literature v tem preglednem članku ne kažejo na uporabnost kratkotrajnih izpostavitev hipoksičnim pogojem za izboljšanje športne sposobnosti. Kljub temu, ima lahko tovrstna dodatna vadba pri posameznih športnikih pozitivne učinke, zato se svetuje individualiziran pristop.

Ključne besede: Hipoksija, aklimatizacija, vadbene metode, intervalna hipoksija

INTRODUCTION

Hypoxic training modalities attracted the interest of sport scientists early in the 1960s when the International Olympic Committee appointed Mexico City (2300 m) as the site for the 19th Olympic Games in 1968. Until then, while obvious examples of substantial human adaptation plasticity as well as the ability of a human organism to adapt to hypoxic stimuli had been observed (ascents to high mountains), little was known about the effects of hypoxia on athletic performance and possible adaptational benefits of hypoxic exposure. Since then, different models of hypoxia application have received significant scientific attention and been used to improve both altitude performance (i.e. altitude pre-acclimatisation) and sea-level athletic performance.

INTRODUCTION TO THE PROBLEM

At present, a vast number of professional and recreational athletes use hypoxic training as a form of additional training to boost their performance (Wilber, 2007). Although the deleterious effects of exposure to altitude have primarily been recognised, the potential beneficial adaptations to hypoxic perturbation have also been seen and pursued. The aim of inducing beneficial adaptations while simultaneously avoiding the detrimental consequences led to the development of several hypoxic training modalities (Levine, 2002). These ranged from traditional altitude training camps where athletes are exposed to chronic continuous hypoxia to brief intermittent hypoxic exposures, repeated in series, all with the intention to improve performance or working capacity at either altitude or sea level (Fig 1.). Although numerous hypoxic training modalities exist, they all rely

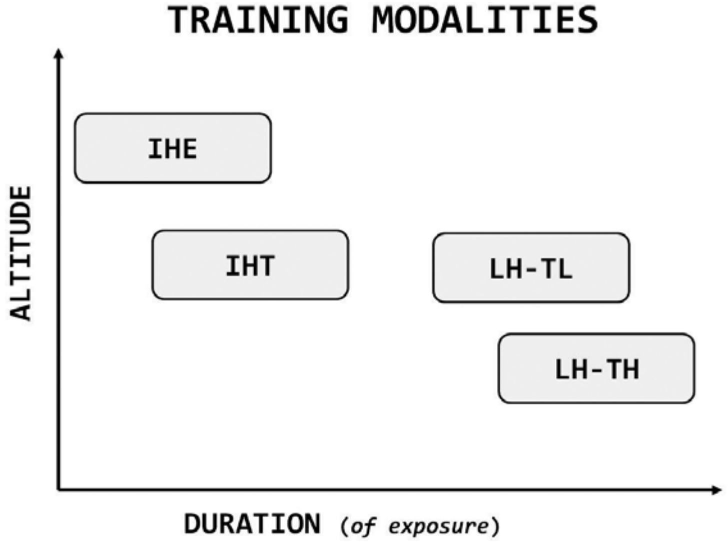

Figure 1. Contemporary hypoxic training modalities. (LH-TH: Live high – train high; LH-TL: Live high – train low; IHT: Intermittent hypoxic training; IHE: Intermittent hypoxic exposures)

on efficient manipulation of the hypoxic dose that is achieved by modifying either the duration of a single exposure, the level of hypoxia or the number of aggregate exposures (Wilber, Stray-Gundersen, & Levine, 2007).

While permanent residence at altitude during moderate altitude sojourns was and still is a popular form of hypoxic training, it is the modalities that employ shorter intermittent exposures which are coming to the forefront of both athletes' and researchers' interest (Millet, Roels, Schmitt, Woorons, & Richalet, 2010). There are several reasons for this. First, while continuous hypoxia can beneficially affect the O_2 flux capacity these benefits can be abated by the negative consequences of chronic hypoxic exposures. In particular, these include dehydration, de-conditioning, altitude-sickness effects, food aversion and especially, with regard to training, the inability to perform high intensity exercises (Mollard, Woorons, Letournel, Lamberto, et al., 2007). All of these factors are usually an outcome of inadequate/insufficient altitude acclimatisation and can consequently result in overreaching and overtraining when the sum of training and hypoxic impulse is outsized (Mollard, Woorons, Letournel, Lamberto, et al., 2007). The relatively minor interruption to both lifestyles and training processes is the next obvious advantage of intermittent protocols. It is clearly beneficial if, for the same intended result, one needs to dedicate two hours per day compared to a whole day. This makes it particularly relevant since athletes already perform large amounts of training volume that necessitate a vast time commitment. This is also in line with logistical difficulties because not everybody has the opportunity to travel to high altitudes. While for longer periods this seems like a viable option when engaging in shorter exposures, the constant travel to and from a terrestrial altitude is not always possible. It is especially for these reasons that the use of altitude simulation is rising in popularity and, in turn, the related technological possibilities are expanding (Muza, 2007).

A decrease in barometric pressure and thus a lowering of partial oxygen pressure (PO_2) occurs when a person ascends to higher altitudes (hypobaric hypoxia). However, as mentioned, traveling to a mountainous region and back is not always very convenient or even possible when different hypoxic training modalities are in use. Moreover, since some regions of the world do not offer an appropriate terrestrial altitude (Australia, Scandinavia) this has led to the fast technological development of hypoxic stimulation facilities and enabled modern athletes to utilise simulated altitude exposures worldwide. Currently, a handful of methods apply different technological methodologies that allow for the simulation of hypoxia (Wilber, 2007). While hypobaric chambers provide the best approximation of natural altitude by making use of both a decrease in PO_2 and barometric pressure, their use is not widespread. This is largely due to the constructional and technological requirements of assembling pressure-resistant facilities. Recently, the use of normobaric simulations of hypoxia using different gas mixture manipulations inducing a decrease in the fraction of inspired O_2 (F_IO_2) without a decrease in barometric pressure (normobaric hypoxia) has been growing in popularity. The most often used and convenient technologies are O_2 filtration or N_2 dilution (Savourey, Launay, Besnard, Guinet, & Travers, 2003; Wilber, 2007). The first method utilises a specific membrane, reducing the molecular O_2 concentration within the ambient air that is drawn from the outside into the application space. The generator pumps the O_2-depleted air to either a room or a custom-made tent. Such O_2 filtration is most commonly used in small personal portable hypoxicators. Nitrogen dilution is a similar method inducing normobaric hypoxia with the simultaneous induction of ambient air and 100% N_2 into the targeted environment. Thus, by introducing excessive N_2 into the ambient air the percentage of O_2 within the gas mixture is reduced to the desired level. This type of application is typically installed in permanent rooms or laboratories. Possible hypoxia applications are presented in Figure 2.

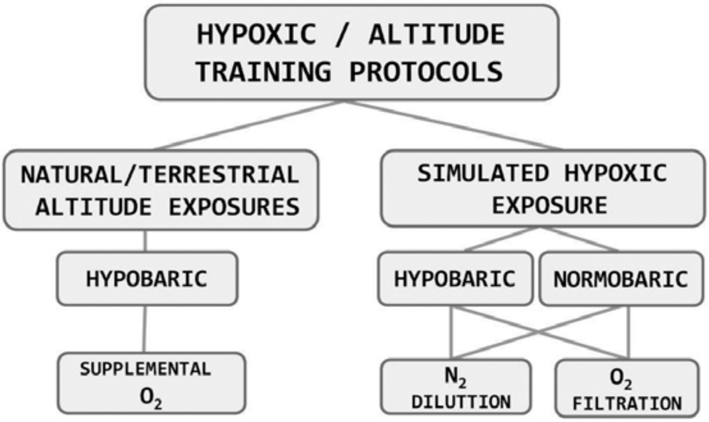

Figure 2. Technological possibilities of hypoxia application.

There are thus multiple options for applying hypoxic stimuli both in relation to the selected modality employed and the type of hypoxia used. Even though for obvious reasons the use of shorter intermittent hypoxic protocols seems superior with regard to time consumption and athlete engagement, as compared to chronic and longer duration protocols, the actual effects and underlying mechanism have still not been established (Bartsch, Dehnert, Friedmann-Bette, & Tadibi, 2008; Hoppeler, Klossner, & Vogt, 2008). Due to the lack of controlled studies investigating the effects of shorter hypoxic modalities, especially on performance at altitude and sea level, further studies are warranted (Lundby, Millet, Calbet, Bartsch, & Subudhi, 2012; Muza, 2007).

The debate regarding the differences in physiological responses to either hypobaric and normobaric exposures to hypoxia is ongoing and the results of contemporary studies do not provide a uniform answer (Millet, Faiss, Pialoux, Mounier, & Brugniaux, 2012). Some studies show that hypobaric hypoxia leads to lower arterial O_2 saturation and greater hypoxemia during exercise compared to normobaric hypoxia (R. Faiss et al., 2013; Savourey et al., 2003), while others suggest that normobaric hypoxia provides a sufficiently faithful surrogate for hypobaric hypoxia exposures (Self, Mandella, Prinzo, Forster, & Shaffstall, 2011). Collectively, it seems that differences do exist in responses to hypobaric and normobaric hypoxia but the magnitude of these differences and their applied values need to be further explored (Millet, Faiss, & Pialoux, 2013). Improvements in the technological advancements and convenience of normobaric hypoxic applications call for an understanding and assessment of the possible normobaric hypoxic modalities' effects.

HYPOXIA-RELATED PHYSIOLOGICAL MECHANISMS FOR IMPROVING PERFORMANCE

While both aerobic and anaerobic processes contribute significantly to exercise performance, the delivery of O_2 is crucial for any exercise lasting more than a few seconds. The main determinants of O_2 delivery to muscle tissue are shown in Fig 3. Also termed the "Oxygen delivery cascade", this pathway represents the flow of ambient O_2 from air to the cellular-muscular level (Mazzeo, 2008). It starts with the transfer of ambient air and is followed by the diffusion of the gas in the lungs.

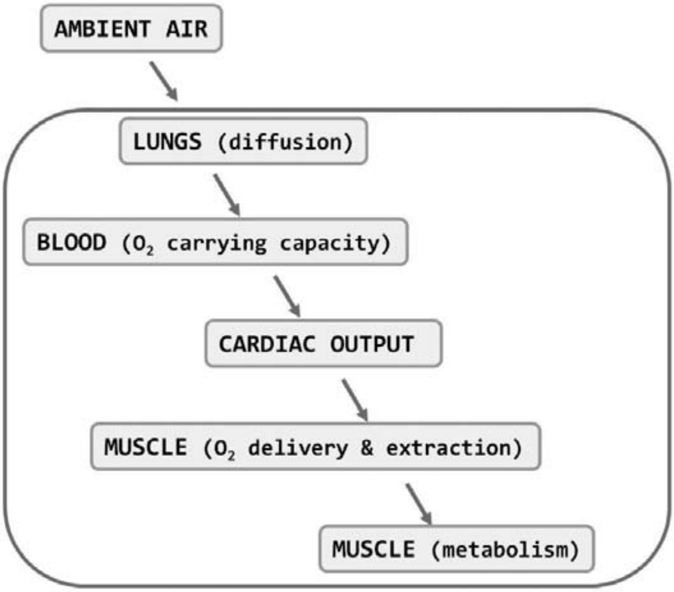

Figure 3. Oxygen pathway from ambient air to muscle tissue.

The oxygen carrying capacity of the blood, cardiac output and muscle blood flow thereafter determine the supply of O_2 to the muscle cells. On the molecular level within muscle cells, the O_2 extraction by the cells and the metabolic efficiency and capacity (i.e.

mitochondria quantity and quality) ultimately limit the amount of energy available for muscle contraction and relaxation. In short, all of the listed factors, although to a different extent, determine endurance performance in both hypoxia and normoxia. Moreover and even more importantly, each step of the cascade can be altered as a response to hypoxic or exercise training stimuli. The selected mechanisms of hypoxia-induced changes related to performance can be seen in Fig 4.

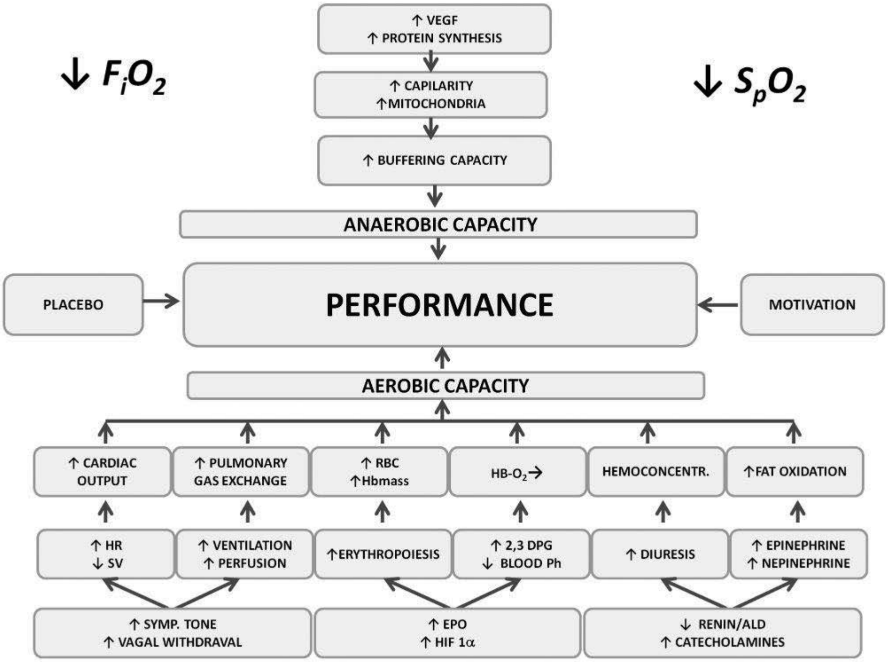

Figure 4. Purported physiological mechanisms accountable for performance improvement following hypoxic training modalities. (VEGF: Vascular endothelial growth factor; HR: Heart rate; SV: Stroke volume; EPO: Erythropoietin; 2,3 DPG: 2,3-Diphosphoglycerate; RBC: Red blood cells; Hb-O2: Oxyhemoglobin dissociation).

The modulation of adaptations to hypoxic perturbation can, in terms of timing, be divided into acute (short term) and chronic (long term). The acute responses occurring immediately after the onset of hypoxic exposure are mainly controlled by the nervous and endocrine systems, thus inducing prompt up-regulations of the pulmonary and cardiovascular systems by sympathetic efferent activity augmentation, vagal stimulation withdrawal and increased catecholamine activity (Mazzeo, 2008). This involves the activation of stress limiting systems, the mobilisation of energy and its transportation to the functional systems. In long-term adaptations, those processes are followed by a phase of gene transcription activation that enables the transition from acute to chronic adaptation. After exposures of a longer duration there is a successive activation of the regulatory genes that consequently lead to enhanced gene coding for the proteins involved in the transport and utilisation of O_2, angiogenesis and haematopoiesis (Sarkar, Banerjee, & Selvamurthy, 2003).

Long-term adaptations at the molecular level are chiefly regulated by the expression of specific target genes that are up-regulated during alternations of O_2 tension. The gene up-regulation is governed by corresponding transcription factors that induce gene transactivation through complex DNA binding and assembling mechanisms (Sarkar et al., 2003). While a wide range of transcriptional factors are suggested to be O_2-regulated, the hypoxia-inducible factors seem to play a crucial role (Semenza, 2009). In particular, the hypoxia-inducible factor 1 alpha (HIF1-α) was the first transcription factor shown to be essential for the hypoxia-induced expression of erythropoietin (EPO) and other hypoxia-related adaptational genes responsible for angiogenesis and metabolic reprograming (Semenza, 2009). While HIF1-α is under a normoxic condition subjected to ubiquitination and proteasomal degradation, during tissue PO_2 reduction this process is inhibited and allows for HIF1-α stabilisation and transcriptional activity (Sarkar et al., 2003).

INTER- AND INTRA-INDIVIDUAL VARIABILITY TO HYPOXIC STIMULI

After the onset of hypoxic exposure, the magnitude and timing of the physiological responses vary among individuals. It has been shown in many studies that some individuals adapt to hypoxic stimulus much faster and more efficiently than others, some of whom may not even be able to acclimatise properly (Mazzeo, 2008). Certain studies (Chapman, Stray-Gundersen, & Levine, 1998; Friedmann et al., 2005) on altitude training protocols have even suggested dividing individuals according to their physiological responses, and named them accordingly ("responders" – "non-responders"). Their results reveal wide inter-individual variability, especially in the hematopoietic response to hypoxic training modalities. The non-responders did not improve their endurance performance or peak oxygen consumption ($\dot{V}O_{2peak}$), although these differences were not related to the changes in EPO production. They suggest that it is not possible to determine a person's response to altitude training solely by monitoring erythropoiesis. The possible genetic determinants of this variability have also been investigated (Jedlickova et al., 2003). The correlations between the EPO gene markers or eight genes involved in EPO regulation and subsequent variations in post-altitude EPO levels have been investigated, but no significant correlation was found. Similarly, no association was noted between I/D-ACE gene polymorphism and adaptation/tolerance to hypoxia (Dehnert et al., 2002). The problem of differentiating between responders and non-responders to altitude training therefore remains unsettled. There is currently no efficient prediction method for individual responses to hypoxic stimuli and performing the protocols and carefully monitoring the responses thus seems to be the only reasonable option available.

The differences between genders in adaptation capacities following altitude exposure are also an important consideration. Possible differences in erythropoiesis and haematological variables are of the greatest interest since this has been postulated as one of the key responses to different hypoxic training protocols (Friedmann-Bette, 2008; Jean, Leal, Kriemler, Meijer, & Moore, 2005). The basic prerequisite for hypoxic training to be effective is normal iron stores. However, due to mechanical haemolysis, sweating, low iron intake and blood loss due to menstruation in female athletes this is often not the case (Chatard, Mujika, Guy, & Lacour, 1999). Trained female athletes frequently experience low haemoglobin (Hb) and haematocrit (HCT) levels due to the above-mentioned chronic depletion of iron stores. The problem can therefore occur if iron levels are insufficient to support the hematopoietic demands. However, it was recently shown that no differences in responses to altitude training between male and female athletes exist if the iron levels are sufficient (Stray-Gundersen, Chapman, & Levine, 2001). Another consideration regarding gender differences is the effect of ovulation. The effects of different phases of the menstrual cycle on altitude acclimatisation responses have not yet been thoroughly described. However, according to the latest findings regarding changes during different phases of the menstrual cycle considerable differences cannot be expected (Smekal et al., 2007). Even though the differences between males and females in responses to altitude training seem negligible, this area calls for further scientific investigation. Accordingly, monitoring of the hormonal and iron status of female athletes before, during and after hypoxic training seems warranted.

CONTEMPORARY HYPOXIC TRAINING MODALITIES

Live High-Train High (LH-TH)

Also called classical altitude training, LH-TH has been a popular modality in the last few decades. Yet the results of controlled studies investigating LH-TH are not uniform (Friedmann-Bette, 2008). The LH-TH modality is almost exclusively performed at terrestrial altitudes where constant altitude residence is conveniently performed as compared to permanent living, training and sleeping within a simulated hypoxic facility. This brings about another possible beneficial influence of this modality i.e. the "training-camp" effect that has been shown to have a possible albeit placebo effect (Bonetti & Hopkins, 2009). LH-TH seeks to take advantage of altitude-acclimatisation-related effects and concomitant use of hypoxia during training to increase the level of exercise-induced hypoxia within the muscles (Richardson et al., 2006). Further, LH-TH is regularly employed by athletes and mountaineers to enhance altitude-specific performance (Kupper & Schoffl, 2009).

The results of the studies investigating the effects of LH-TH are not uniform, yet it has been shown that some benefits can be expected. Since permanent residence allows for efficient acclimatisation, performance or working capacity at altitude has been shown to improve (Horstman, Weiskopf, & Jackson, 1980). However, findings regarding the effects of LH-TH on sea-level performance are more diverse. Some controlled studies have revealed favourable effects, namely increases in $\dot{V}O_{2peak}$ (Levine & Stray-Gundersen, 1997) and maximal performance in an incremental test (Burtscher, Nachbauer, Baumgartl, & Philadelphy, 1996). In contrast, other studies have not shown any favourable effects on aerobic capacity (Gore, Hahn, Burge, & Telford, 1997) or even pointed to a decrease in mean running velocity during a supramaximal test following LH-TH (Bailey et al., 1998). The acclimatisation induced by continuous residence and training at altitude has been demonstrated to result in an augmentation of the total haemoglobin mass (Heinicke, Heinicke, Schmidt, & Wolfarth, 2005) and also to be significantly correlated with concomitant changes in $\dot{V}O_{2peak}$ (Levine & Stray-Gundersen, 1997). Regarding non-haematological parameters, although no enhancement of muscle tissue oxidative capacity has been observed (Saltin et al., 1995) the buffering capacity has been shown to increase significantly following two weeks of LH-TH at altitudes between 2,100 – 2,700 m (Mizuno et al., 1990).

The main drawbacks of LH-TH training are decrements in exercise intensities due to impaired aerobic capacity at altitude and a subsequent lower mechanical and neural training load arising from an inability to perform exercise of the highest intensity (Levine & Stray-Gundersen, 1997). Since LH-TH is performed at a natural altitude individual adjustments of exposure altitude are not possible. While this is an obvious weakness in light of the large individual variability observed in response to hypoxic perturbations (Chapman et al., 1998), it can be partially adjusted by repeatedly modifying and regularly monitoring the intensity of individual training so as to avoid possible overreaching and subsequent detraining (Friedmann, Bauer, Menold, & Bartsch, 2004).

Live High-Train Low (LH-TL)

Bearing in mind the above-mentioned detrimental effects of chronic hypoxic exposures, especially for training and conditioning, the LH-TL protocol was introduced in 1997 (Levine & Stray-Gundersen, 1997). Their study showed that, following the tested protocol, subjects from both LH-TL and LH-TH groups significantly increased their Hb, erythrocyte volume, and $\dot{V}O_{2peak}$. However, only the LH-TL group significantly increased the 5000-m running time. This confirmed their premise of the ability of LH-TL to concomitantly enable sufficient acclimatisation to improve the O_2 flux while maintaining the benefits of sea-level training.

Studies investigating LH-TL at a natural altitude have shown that if the modality is performed for at least four weeks at altitudes between 2,500 to 2,800 m, subsequent augmentation of both red cell mass and $\dot{V}O_{2peak}$ can be seen, thus leading to improved performance (Stray-Gundersen & Levine, 2008). Greater variability can be seen in the findings of studies dealing with simulated LH-TL (Richalet & Gore, 2008). Regarding the haematological benefits, the results consistently vary according to both the cumulative and daily hypoxic dose. Studies employing longer daily exposures ranging between 12-17 h·day-1 revealed increases in red cell volume (Robach et al., 2006) and serum transferrin (Brugniaux et al., 2006). In contrast, studies investigating shorter daily exposures (6-12 h·day-1) during LH-TL did not show any modifications of haemoglobin mass (Saunders et al., 2004) or reticulocyte count (Ashenden, Gore, Dobson, & Hahn, 1999). Even though the main mechanism postulated as being responsible for performance improvements has been reasoned to be the blood-related enhancements of O_2 flux capacity (Levine & Stray-Gundersen, 1997), a number of other hypoxia-inducible factors (HIF-1; HIF-2) driving mechanisms on the molecular level were shown to occur (Gore, Clark, & Saunders, 2007). These include improvements in exercise efficiency related to the augmented muscle cells' mitochondrial efficiency, improved acid base cell status regulation, improved muscle cell metabolic efficiency and increased muscle buffering capacity (Gore et al., 2001). Moreover, improvements in hypoxic ventilatory response (Townsend et al., 2002) and muscle Na-K ATPase activity have also been documented (Aughey et al., 2006).

Besides improvements in altitude performance, the main incentive is to improve performance back at sea level. While most studies employing a natural LH-TL modality reveal a positive benefit for subsequent sea-level performance (Stray-Gundersen & Levine, 2008), the results of simulated LH-TL studies have produced inconsistent findings (Richalet & Gore, 2008). Whilst some studies showed increases in both $\dot{V}O_{2peak}$ (Robach et al., 2006) and time-trial performance (Hahn et al., 2001), other studies of both elite runners and cyclists did not find any significant improvements in sea-level performance following simulated LH-TL (Clark et al., 2004; Neya, Enoki, Kumai, Sugoh, & Kawahara, 2007). When employing the LH-TL modality, the optimal daily hypoxic exposure duration seems to be between 16 – 22 hours and can be reduced when the main aims are non-haematological benefits (Millet et al., 2010). While the presented results collectively show that LH-TL should also be beneficial for elite athletes, a very recent study (Siebenmann et al., 2012) could not identify any significant effect following four weeks of LH-TL. Those authors employed a strict, double-blind placebo-controlled study design and, even though the collective hypoxic or placebo hypoxic exposure exceeded 440 hours, there were no significant gains in performance following LH-TL compared to a placebo LH-TL. They suggested that the placebo effect could be at least partly responsible for the beneficial outcomes of other studies that were not designed in a placebo-controlled, double-blind fashion (Siebenmann et al., 2012).

Intermittent hypoxic training (IHT)

While intermittent applications of hypoxia stimuli are used in all modalities except LH-TH, the word "intermittent" in IHT refers to short periods of hypoxia (minutes to two hours) interspersed between normoxia. It has been reasoned that similar effects can be expected as with chronic ones, without the detrimental effects of the latter, by applying brief hypoxic exposures. In particular, IHT refers to use of both hypoxic and training impulses concomitantly. The premise of IHT lies in utilisation of the hypoxic stimuli during the training to surplus the normal training load. Since aerobic capacity decays inversely with increasing altitude, the same absolute workload represents a higher relative workload when training is performed under hypoxic conditions (Mollard, Woorons, Letournel, Cornolo, et al., 2007). This therefore induces specific signalling effects on the molecular level in muscular tissue, possibly leading to beneficial changes in muscle cell properties relevant to performance (Hoppeler et al., 2008). These adaptations are the fundamental aim of IHT since the duration of the hypoxic impulse is insufficient to enable the occurrence of haematological beneficial changes in red blood cell numbers or total haemoglobin mass (Millet et al., 2010). IHT is usually performed for no longer than one to two hours per day. Therefore, when employing IHT the main aim of the training should not be the haematological benefits but an improvement in the efficiency and working capacity of muscles. Moreover, even though the hypoxic exposure duration is shorter, ventilatory benefits, namely higher ventilatory levels, have already been shown following IHT (Dufour et al., 2006). In addition, the fact that IHT only employs short hypoxic periods has at least two advantages. First, the avoidance of the deleterious effects of chronic high altitude exposures on muscle tissue (Green, Sutton, Cymerman, Young, & Houston, 1989) and, second, it only involves a slight disturbance to an athlete's usual daily routine. However, as has already been shown, the amplified training impulse induced by a concomitant training load and hypoxia can also swiftly lead to overreaching or overtraining if the total training load is not adjusted accordingly (Ventura et al., 2003). In addition, unacclimatised exposures to severe hypoxia, even brief ones, should be avoided to prevent cellular damage related to oxidative stress.

For convenience, IHT is habitually performed in simulated hypoxia under either a normobaric or hypobaric condition. The simulated altitude used in IHT usually varies between 2,500 to 5,000 m as altitudes ≤ 2,500 m have little effect and at altitudes ≥ 5,000 m a sufficient exercise training load is hard to achieve for all but the really top acclimatised athletes (Muza, 2007). Regardless of the mode of hypoxia, the results of studies show a general tendency of improving both performance and $\dot{V}O_{2peak}$ under hypoxic conditions. On the other hand, the majority of studies have not found any advantages of IHT training for sea-level performance (Hoppeler et al., 2008). Table 1 summarises the studies investigating IHT performed in normobaric hypoxia on selected markers of performance. Although there is a tendency for beneficial results when employing greater IHT training duration, a study by Bailey (Bailey, Castell, Newsholme, & Davies, 2000) showed that twelve 30-minute sessions interspersed over four weeks have the ability to improve the normoxic $\dot{V}O_{2peak}$. Similar findings have been shown in trained runners employing 30 IHT sessions over a period of 6 weeks (Dufour et al., 2006). However, findings from our lab (Debevec et al., 2010) did not show any beneficial effect of moder-

Table 1. Study designs and data metrics of the studies investigating normobaric IHT.

IHT training	Condition / Subjects	Outcome metric	Metric response	Conclusions	Reference
≈120 min+40 min 5·week^{-1}/6 weeks Normal training	C: F_IO_2= 0.209 H: F_IO_2= 0.145 Trained runners	$VO_{2peakNORMO}$ T_{lim}	C: + 1.2 % H: +5.3 % ↑ C: + 10 % H: +35 % ↑	IHT is superior over normoxic training	(Dufour, et al., 2006)
60 min 6·week^{-1}/3 weeks 80% VO_{2peak}	C: F_IO_2= 0.209 H: F_IO_2= 0.12-0.10 Untrained	$VO_{2peakHYPO}$ HVR	C: - 0.2 % H: +4.8 % C: ≈ H: +54 %	IHT induces hypoxia preacclimatization	(Benoit, et al., 1992)
120 min 6·week^{-1}/3 weeks 75 % VO_{2peak}	C: F_IO_2= 0.209 H: F_IO_2= 0.12-0.10 Untrained	$VO_{2peakNORMO}$ $VO_{2peakHYPO}$	C: + 0.5 % H: + 6.4 % C: + 1.9 % H: + 11 %	IHT improves $VO_{2peakHYPO}$ if performed at the same relative WL	(Desplanches, et al., 1993)
30 min 3·week^{-1}/4 weeks 80% HR_{max}	C: F_IO_2= 0.209 H: F_IO_2= 0.135 Untrained active	$VO_{2peakNORMO}$ $W_{maxNORMO}$	C: + 4 % H: + 13.5 % ↑ C: + 7 % ↑ H: + 4.6 % ↑	IHT improved normoxic aerobic capacity	(Bailey, Castell, Newsholme, & Davies, 2000)
30 min 5·week^{-1}/6 weeks 75 % VO_{2peak}	C: F_IO_2= 0.209 H: F_IO_2= 0.12 Untrained	$VO_{2peakNORMO}$ $VO_{2peakHYPO}$	C: + 9.5 % ↑ H: + 11.1 % ↑ C: + 3.4 % ↑ H: + 7.2 % ↑	Similar performance benefits as C but improved $VO_{2peakNORMO}$	(Geiser, et al., 2001)
30 min 3·week^{-1}/8 weeks 75 % VO_{2peak} Single leg	C: F_IO_2= 0.209 H: F_IO_2= 0.135 Untrained	$VO_{2peakNORMO}$ T_{lim}	C: + 13 % ↑ H: +11 % ↑ C: + 400 % H: + 510 %	No functional benefit of IHT	(Melissa, MacDougall, Tarnopolsky, Cipriano, & Green, 1997)
12.5 min 3·week^{-1}/5 weeks High intensity	C: F_IO_2= 0.209 H: F_IO_2= 0.153 Trained swimmers	$VO_{2peakNORMO}$	C: +5.6 % ↑ H: +3.8 % ↑	No additive effect of IHT	(Truijens, Toussaint, Dow, & Levine, 2003)
3·30 (20, 10) min 3·week^{-1}/4 weeks 80 &50% VO_{2peak}	C: F_IO_2= 0.209 H: F_IO_2= 0.15 Team sport players	$VO_{2peakNORMO}$ $W_{maxNORMO}$	C: +8 % ↑ H: +7.2 % ↑ C: +17 % ↑ H: +15.5 % ↑	No additive effect of IHT	(Morton & Cable, 2005)
60 min 5·week^{-1}/4 weeks 50% VO_{2peak}	C: F_IO_2= 0.209 H: F_IO_2= 0.120 Untrained	$VO_{2peakNORMO}$ $VO_{2peakHYPO}$	C: + 18 % ↑ H: +2 % C: +1 % H: - 8 %	IHT did not enhance aerobic capacity in neither condition	(Debevec, et al., 2010)

C: Control group; H: IHT group; F_IO_2: Fraction of inspired oxygen; $VO_{2peakNORMO}$: maximal aerobic capacity in normoxia; T_{lim}: time to exhaustion; $VO_{2peakHYPO}$: maximal aerobic capacity in hypoxia; HVR: hypoxic ventilatory response; $W_{maxNORMO}$: peak power output in normoxia; $W_{maxHYPO}$: peak power output in hypoxia; + increase; - decrease; ↑ significant ($P < 0.05$).

ate intensity endurance training in hypoxia as compared to the same relative intensity normoxic training. Very recent data (Faiss et al., 2013) suggest that high intensity interval training performed in normobaric hypoxia might be superior to high intensity training performed in normoxia especially in relation to intermittent high intensity efforts.

Regarding the effects of normobaric IHT on performance in hypoxia, two studies reveal a beneficial pre-acclimatisation effect. Namely, the study by Benoit et al. (Benoit et al., 1992) shows that, although subsequent performance was similar between groups, the HVR was only significantly increased in the IHT group, thus revealing the potentially beneficial ventilatory acclimatisation effect. The second study points to the benefits of IHT over normoxic training on hypoxic $\dot{V}O_{2peak}$ stipulating that the training was performed with the same relative workload in both conditions (Desplanches et al., 1993). On the other hand, some studies did not find any significant additional effect of IHT on performance metrics on either normoxic $\dot{V}O_{2peak}$, Wmax or time to exhaustion in both trained and untrained subjects (Melissa, MacDougall, Tarnopolsky, Cipriano, & Green, 1997; Morton & Cable, 2005; Truijens, Toussaint, Dow, & Levine, 2003). The only study investigating the IHT effects in both normoxic and hypoxic conditions was performed by Geiser et al. (Geiser et al., 2001). It did not find any significant differences between IHT and normoxic training, besides a significantly greater increase in normoxic $\dot{V}O_{2peak}$ in the IHT group compared to the control.

As mentioned, the main mechanism responsible for the possible improvements following IHT seems to be the changes on the molecular level in muscle tissue. Since the training response is always modulated through an integrated signalling pattern induced by mechanical load, metabolic disturbance, neuronal activation and hormonal adaptations, the identifying of specific IHT response pathways is complex (Fluck & Hoppeler, 2003). During hypoxia, the transcriptional signalling and subsequent adaptations are governed at the molecular level by HIF-1α related processes that not only master the regulatory genes for erythropoiesis but also glycolysis and pH regulation (Lee, Bae, Jeong, Kim, & Kim, 2004). The subsequent advantageous effects include greater buffering capacity, lactic acid tolerance and improved muscle efficiency (Benoit et al., 1992). As expected, no haematological benefits have been reported from IHT studies, mostly due to insufficient daily and aggregate hypoxic doses to stimulate erythrocyte production stimulation (Emonson, Aminuddin, Wight, Scroop, & Gore, 1997; Truijens et al., 2003).

Intermittent hypoxic exposures (IHE)

Similarly to IHT, intermittent hypoxic exposures (IHE) refer to the use of brief hypoxic exposures as a means for improving well-being or performance. The main difference with regard to IHT is that all hypoxic exposures are performed at rest during the IHE (i.e. without any exercise training). For the purposes of clarity, the IHE modality can be divided into two models of application. The first refers to the use of brief (3 – 6 minutes) and relatively high levels of hypoxia (F_IO_2 = 0.15 – 0.09) interspersed with periods of normoxia of a similar duration. This model was introduced and broadly used in Eastern European states for both clinical applications and performance enhancements (Serebrovskaya, 2002). Typically, normobaric hypoxia is used for this model since even the simulation of altitude using a hypobaric chamber does not readily permit constant changes in PO_2. The second IHE model relies on intermittent applications of longer hypoxic exposures that last between 30 minutes to 5 hours. This model was prepared for high-altitude expedition pre-acclimatisation protocols with the aim of reducing the acclimatisation time on one hand and improving performance at altitude on the other (Richalet et al., 1992). Owing to the longer constant exposures, both simulated normobaric and hypobaric hypoxia may be used depending on the technological options. Both models seem to be a promising means for hypoxia application, especially with regard to time consumption and convenience. However, the results regarding their effects on performance and selected physiological variables are less appealing (Bartsch et al., 2008; Muza, 2007).

The accountable physiological mechanism relates to augmentation of respiratory sensitivity, neural effects, and improved mitochondrial activity (Serebrovskaya, 2002). This indicates that the primary adaptational aims are not haematological, but rely on augmented ventilation and substrate utilisation (Muza, Beidleman, & Fulco, 2010). Even though one of the early studies showed that significant blood-related benefits in a reticulocyte count, Hb and HCT can be expected when employing just nine 90-minute exposures to hypobaric hypoxia during a period of three weeks (Rodriguez et al., 1999), subsequent studies did not confirm those findings (Hinckson, Hopkins, Downey, & Smith, 2006; Julian et al., 2004), thus demonstrating that a higher hypoxic dose (i.e. a combination of hypoxia level and duration) is required to promote the erythropoietic response.

As noted, results regarding the effects of IHE on performance remain elusive. Table 2 summarises the studies investigating the normobaric IHE modality employing brief alternations between hypoxic and normoxic exposures. As can be seen, only three out of eight studies found significant benefits of IHE for performance metrics. Whilst the studies by Wood et al. (Wood, 2006) and Hamlin et al. (Hamlin & Hellemans, 2007) showed significant improvements following 21 (60-min) and 15 (90-min) sessions of IHE in sprint time and 3,000 m run time, respectively. Interestingly, the study by Shatilo et al. (Shatilo, Korkushko, Ischuk, Downey, & Serebrovskaya, 2008) found benefits in submaximal working capacity after only ten 20-minute sessions of relatively mild IHE (capillary oxygen saturation (S_pO_2) = 85%). In contrast, other controlled studies employing a blind design did not show any benefit for either aerobic (Julian et al., 2004) or anaerobic (Tadibi, Dehnert, Menold, & Bartsch, 2007) performance at sea level and at moderate

Table 2. Study designs and data metrics of the studies investigating short normobaric IHE.

Subjects	IHE protocol	Outcome metric	Metric response	Conclusions	Reference
Team sport players	$\sum$ 60 min, 6:4 $7\cdot week^{-1}$/3 weeks S_pO_2= 90 - 77 %	V_{max} T_{sprint}	C: - 0.3 % H: + 1.7 % ↑ C: - 0.5 % H: - 5.1 % ↑	Substantial improvement in sprint performance	(Wood, Dowson, & Hopkins, 2006)
Active elderly	$\sum$ 20 min, 5:5 10 days S_pO_2= 85 - 86 %	W_{sub} BP	H: 11.3 % ↑ H: - 7.9 mmHg ↑	IHE has beneficial effects on work capacity and hemodynamics	(Shatilo, Korkushko, Ischuk, Downey, & Serebrovskaya, 2008)
Multisport athletes	$\sum$ 90 min, 5:5 $5\cdot week^{-1}$/3 weeks F_IO_2= 0.13-0.10	T_{3000}	H: - 2.3 % ↑ C: - 0.6 %	IHE is likely beneficial for multisport athletes	(Hamlin & Hellemans, 2007)
Elite rowers	$\sum$ 90 min, 6:4 $7\cdot week^{-1}$/3 weeks S_pO_2= 90 - 80 %	$W_{mean5000}$ $W_{mean500}$	C: ≈ H: + 0.6 % C: ≈ H: - 2.2 %	IHE is unlikely to have a major effect on performance	(Hinckson, Hopkins, Downey, & Smith, 2006)
Elite runners	$\sum$ 70 min, 5:5 $5\cdot week^{-1}$/4 weeks F_IO_2= 0.12-0.10	$VO_{2peakNORMO}$ T_{lim}	C: ≈ H: ≈ C: ≈ H: ≈	Not a sufficient stimulus to enhance performance	(Julian, et al., 2004)
Trained runners	$\sum$ 60 min, 6:4 $7\cdot week^{-1}$/2 weeks F_IO_2= 0.11-0.10	$VO_{2peakNORMO}$ W_{max}	C: - 0.3 % H: + 2,2 % C: - 0.2 % H: + 2.4 %	IHE has no effect on aerobic or anaerobic performance	(Tadibi, Dehnert, Menold, & Bartsch, 2007)
Team sport players	$\sum$ 90 min $7\cdot week^{-1}$/2 weeks F_IO_2= 0.15-0.10	V_{max} T_{sprint}	C: < 1 % H: < 1 % C: ≈ H: ≈	IHE is not suggested for games preparation	(Hinckson, Hamlin, Wood, & Hopkins, 2007)
Untrained active	$\sum$ 60 min, 5:3 $5\cdot week^{-1}$/4 weeks F_IO_2= 0.12-0.09	$VO_{2peakNORMO}$ $VO_{2peakHYPO}$ T_{lim} $T_{lim\ HYPO}$	C: +18 % ↑ H: +19 % ↑ C: ≈ H: ≈ C: +110 % ↑ H: +100 % ↑ C: H: ≈	No additional effect of IHE protocol on performance in normoxia and hypoxia	(Mekjavic, Debevec, Amon, Keramidas, & Kounalakis, 2012)
Team sport players	$\sum$ 60 min, 6:4 $7\cdot week^{-1}$/2 weeks F_IO_2= 0.13-0.10	V_{max} T_{sprint}	C: ≈ H: ≈ C: ≈ H: ≈	No effect of IHE on altitude impaired performance	(Hamlin, Hinckson, Wood, & Hopkins, 2008)

C: Control group; H: IHE group; ∑: total IHE time; Hypo:Normo exposure; F_IO_2: Fraction of inspired oxygen; S_pO_2 : Blood O_2 saturation; V_{max}: maximal speed; T_{sprint}: sprint time; W_{sub}: submaximal work; BP: Blood pressure; T_{3000}: 3000 meters run time; $W_{mean5000}$: mean power during the 5000 m test ; $W_{mean500}$: mean power during the 500 m test; $VO_{2peakNORMO}$: maximal aerobic capacity in normoxia; $VO_{2peakHYPO}$: maximal aerobic capacity in hypoxia; T_{lim}: time to exhaustion; $T_{lim\ HYPO}$: time to exhaustion in hypoxia; ; TT: time trial; W_{max}: peak power output; + increase; - decrease; ≈ no change; ↑ significant ($P < 0.05$).

Table 3. Study designs and data metrics of the studies investigating long normobaric IHE.

Subjects	**IHE protocol**	**Outcome metric**	**Metric response**	**Conclusions**	**Reference**
Trained athletes	120 min 3·week^{-1}/5 weeks F_IO_2= 0.15-0.10	T_{lim} VO_2	C: + 0.4 min H: + 1 min ↑ C: - 0.3 ml·kg^{-1}·min^{-1} H: - 2.3 ml·kg^{-1}·min^{-1}↑	IHE can be beneficial depending on the training period	(Burtscher, Gatterer, Faulhaber, Gerstgrasser, & Schenk, 2010)
Trained runners	180 min 7·week^{-1}/2 weeks F_IO_2= 0.123	$VO_{2peakNORMO}$ T_{3000}	C: ≈ H: + 0.7 % C: + 0.8 % H: - 1.1 %	IHE can augment running economy and thus enhance performance	(Katayama, et al., 2004)
Trained runners	60 min 7·week^{-1}/1 week F_IO_2= 0.123 F_IO_2= 0.155	V_{EHYPO} HVR	C: ≈ H: ≈ C: ≈ H: ↑	No effects of IHE on altitude exercise ventilation.	(Katayama, et al., 2007)
Untrained active	180 min 7·week^{-1}/1 week F_IO_2= 0.12	TT_{HYPO} S_pO_{2HYPO}	C: - 12 % H: + 2.7 % C: ≈ H: ≈	Seven IHE exposures does not improve altitude performance	(Beidleman, et al., 2009)
Trained cyclists	60 min 7·week^{-1}/1 week F_IO_2= 0.125	$W_{meanHYPO}$	H: ≈ compared to C	No positive effect on altitude performance	(Faulhaber, Gatterer, Haider, Patterson, & Burtscher, 2010)
Untrained active	240 min 4 days F_IO_2= 0.12	$T_{limHYPO}$	C: ≈ H: ≈	Enhanced ventilation but no effect on time to exhaustion	(Debevec & Mekjavic, 2012)

C: Control group; H: IHE group; F_IO_2: Fraction of inspired oxygen; T_{lim}: time to exhaustion; VO_2: exercise oxygen consumption; $VO_{2peakNORMO}$: maximal aerobic capacity in normoxia; T_{3000}: 3000 meters run time; V_{EHYPO}: Minute ventilation in hypoxia; HVR: hypoxic ventilatory response; TT_{HYPO}: Hypoxic time trial performance; S_pO_{2HYPO}: Capillary oxyhemoglobin saturation in hypoxia; $W_{meanHYPO}$: mean power in hypoxia; $T_{limHYPO}$: time to exhaustion in hypoxia; + increase; - decrease; ≈ no change; ↑ significant ($P < 0.05$).

altitude (Hamlin, Hinckson, Wood, & Hopkins, 2008). In addition, a recent study by our lab also did not reveal any additive effect of IHE on normoxic and hypoxic $\dot{V}O_{2peak}$ and endurance performance (Mekjavic, Debevec, Amon, Keramidas, & Kounalakis, 2012).

Similarly, studies investigating a longer continuous IHE model do not show uniform results. Since this IHE model can be applied using either simulated normobaria or hypobaria, the related discrepancies have to be taken into account. In particular, when IHE was applied using hypobaric hypoxia the majority of studies showed possible benefits for performance (Beidleman et al., 2003; Beidleman et al., 2008) and ventilatory acclimatisation (Katayama, Sato, Ishida, Mori, & Miyamura, 1998). In contrast, the results of normobaric IHE studies (Table 3) do not suggest that normobaric IHE is beneficial to performance (Beidleman et al., 2009; Debevec & Mekjavic, 2012; Faulhaber, Gatterer, Haider, Patterson, & Burtscher, 2010; Katayama et al., 2007). However, a study by Burtscher et al. (2010) showed that three 2-hour IHE sessions per week for 5 weeks can improve running performance and exercise economy, although the benefits tend to depend on an athlete's training phase. Likewise, the ability of longer IHE to improve exercise economy was also reported by Katayama et al. (2004).

According to the current findings, the efficacy of both continuous and brief IHE is not firmly established. The main source of discrepancies in the findings and complex pooling of the IHE studies results is the hypoxic dose and its modulation (Bartsch et al., 2008). Namely, the exposure times, level of hypoxia and the duration of the interventions are the main determinants of the hypoxic dose. Thus, the pivotal question regarding the minimal IHE dose for inducing beneficial adaptations remains unanswered. Further strictly controlled studies seem necessary to clarify the unsettled issues.

COMBINING HYPOXIC MODALITIES

Since all modalities manipulate the amount and application of the hypoxic dose, it is not surprising that different combinations exist within the protocols. Namely, the rationale of combining the hypoxic training modalities in such a manner is that they allow for only those parts that are presumably beneficial to be utilised. While there are many possibilities, a recent comprehensive review (Millet et al., 2010) suggested two training modalities' modifications. Since LH-TL has been shown to be an efficient modality for improving even elite athletes' performance at sea level (Wilber et al., 2007), they use it as a baseline modality. They suggest alternating the nights spent at hypoxia with those ones in normoxia at a ratio of 5-2 or 6-1. Moreover, since beneficial alternations within the muscle on the molecular level have been established using IHT, they suggest substituting two or three training sessions per week at sea level with training in hypoxia. This combination would presumably hold the greatest value for intermittent sport athletes by benefiting both their aerobic and anaerobic exercise ability (Millet et al., 2010). The combination of LH-TL and IHT was already shown to be effective in a recent study by Robertson et al. (Robertson, Saunders, Pyne, Gore, & Anson, 2010). They compared the effects of a 3-week-long protocol of combining LH-TL/IHT versus IHT only. Compared to IHT, the LH-TL/IHT combination triggered a substantially improved $\dot{V}O_{2peak}$, total Hb mass and time-trial performance. They concluded that the combination of LH-TL/IHT appears to be a promising mixture of hypoxic modalities for enhancing physiological capacity.

Pre-exposures for altitude acclimatisation and attenuation of altitude-induced reduction of working capacity also often consist of different hypoxic modality combinations. They usually combine both IHE models with concomitant IHT (Muza, 2007), even though there were reportedly no significant differences between the inclusion or exclusion of IHT in a prolonged IHE model (Beidleman et al., 2004). In contrast, according to a recent review (Burtscher, Brandstatter, & Gatterer, 2008) while the effects of IHE with or without IHT may be similar for shorter duration protocols when longer protocols are used the inclusion of IHT may prove beneficial. These benefits can be reflected in both increased performance at altitude as well as a reduction of altitude-related detrimental effects (Burtscher et al., 2008).

CONCLUSION AND PERSPECTIVE

The management of training and hypoxic stimulus is a complex process. It is important to constantly monitor the effects provided by both and adjust the intensities and loads of the training as well as the hypoxic dose to the obtained test results to avoid overtraining on one hand and insufficient adaptational impulses on the other. Collectively, the findings on the performance effects of different hypoxic training modalities are inconclusive. While some studies have shown the ability of all modalities to effectively boost performance, others have not. A recent meta-analysis of the effects of different hypoxic training modalities on sea-level performance revealed that LH-TL seems to be the most effective model for inducing beneficial changes in performance (Bonetti & Hopkins, 2009), while other modalities i.e. LH-TH, IHT and IHE can also be beneficial, especially for sub-elite athletes and untrained subjects. The possible results of a specific protocol therefore have to be taken into account when deciding which one to use and thereafter integrating them into the basic athletic training. The differences in individual responses to altitude training protocols must be carefully monitored to ensure the best possible benefits. It has been reasoned that a placebo or a nocebo effect could have led to discrepancies among the studies' outcomes (Bonetti & Hopkins, 2009; Siebenmann et al., 2012). Accordingly, there is an obvious need for more well-designed (double-blind, cross-over design) studies performing functional tests in both hypoxia and normoxia and investigating the effects of the hypoxic modalities following the cessation of the training (e.g. de-acclimatisation) in both elite athletes and untrained subjects. Therefore, future studies are needed to define the least time-consuming and most efficient protocol.

In conclusion, the studies investigating different hypoxic modalities have unequivocally established that a sufficient hypoxic dose can in some but not all individuals improve maximal aerobic capacity and other performance-related physiological variables at sea level and altitude and can thus be advantageous for performance (Levine & Stray-Gundersen, 2006; Wilber, 2007; Wilber et al., 2007). However, it is currently unknown whether similar effects can be achieved by employing hypoxic training modalities using shorter exposures ($< 6\ \mathrm{h \cdot day^{-1}}$). Based especially on the previous well-controlled studies, it would seem likely that these protocols do not provide a robust response in terms of performance enhancement. The beneficial findings of certain studies can most probably be attributed, at least partly, to a placebo effect.

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