REVIEW ARTICLE

Sports Med 2010; 40 (1): 1-25
0112-1642/10/0001-0001/$49.95/0

Combining Hypoxic Methods for Peak Performance

Gregoire P. Millet,[1] *B. Roels*,[2] *L. Schmitt*,[3] *X. Woorons*[4] and *J.P. Richalet*[4]

1 ISSUL, Institute of Sport Science, University of Lausanne, Lausanne, Switzerland
2 ORION, Clinical Services Ltd, London, UK
3 National Nordic Ski Centre, Prémanon, France
4 Université Paris 13, Laboratoire`Réponses cellulaires et fonctionnelles à l'hypoxie', EA2363 ARPE, Bobigny, France

Contents

Abstract

New methods and devices for pursuing performance enhancement through altitude training were developed in Scandinavia and the USA in the early 1990s. At present, several forms of hypoxic training and/or altitude exposure exist: traditional 'live high-train high' (LHTH), contemporary 'live high-train low' (LHTL), intermittent hypoxic exposure during rest (IHE) and intermittent hypoxic exposure during continuous session (IHT). Although substantial differences exist between these methods of hypoxic training and/or exposure, all have the same goal: to induce an improvement in athletic performance at sea level. They are also used for preparation for competition at altitude and/or for the acclimatization of mountaineers.

The underlying mechanisms behind the effects of hypoxic training are widely debated. Although the popular view is that altitude training may lead to an increase in haematological capacity, this may not be the main, or the only, factor involved in the improvement of performance. Other central (such as ventilatory, haemodynamic or neural adaptation) or peripheral (such as muscle buffering capacity or economy) factors play an important role.

LHTL was shown to be an efficient method. The optimal altitude for living high has been defined as being 2200–2500 m to provide an optimal erythropoietic effect and up to 3100 m for non-haematological parameters. The optimal duration at altitude appears to be 4 weeks for inducing accelerated erythropoiesis whereas <3 weeks (i.e. 18 days) are long enough for beneficial changes in economy, muscle buffering capacity, the hypoxic ventilatory response or Na^+/K^+-ATPase activity. One critical point is the daily dose of altitude. A natural altitude of 2500 m for 20–22 h/day (in fact, travelling down to the valley only for training) appears sufficient to increase erythropoiesis and improve sea-level performance. 'Longer is better' as regards haematological changes since additional benefits have been shown as hypoxic exposure increases beyond 16 h/day. The minimum daily dose for stimulating erythropoiesis seems to be 12 h/day. For non-haematological changes, the implementation of a much shorter duration of exposure seems possible.

Athletes could take advantage of IHT, which seems more beneficial than IHE in performance enhancement. The intensity of hypoxic exercise might play a role on adaptations at the molecular level in skeletal muscle tissue. There is clear evidence that intense exercise at high altitude stimulates to a greater extent muscle adaptations for both aerobic and anaerobic exercises and limits the decrease in power. So although IHT induces no increase in $\dot{V}O_{2max}$ due to the low 'altitude dose', improvement in athletic performance is likely to happen with high-intensity exercise (i.e. above the ventilatory threshold) due to an increase in mitochondrial efficiency and pH/lactate regulation. We propose a new combination of hypoxic method (which we suggest naming Living High-Training Low and High, interspersed; LHTLHi) combining LHTL (five nights at 3000 m and two nights at sea level) with training at sea level except for a few (2.3 per week) IHT sessions of supra-threshold training. This review also

provides a rationale on how to combine the different hypoxic methods and suggests advances in both their implementation and their periodization during the yearly training programme of athletes competing in endurance, glycolytic or intermittent sports.

To date, several forms of hypoxic training and/or altitude exposure exist: traditional 'live high-train high' (LHTH), contemporary 'live high-train low' (LHTL or $LH + TLO_2$) or 'live low-train high' (LLTH) approaches.

More recently, interest has focused on the potential of intermittent hypoxic methods (figure 1) using intermittent hypoxic exposure during rest (IHE), during continuous sessions (IHT), during interval-training (IHIT) or 'live high-train low and high' (LHTLH). Although substantial differences exist between these types of hypoxic training and/or exposure, all have the same primary goal: to induce an improvement in athletic performance at sea level. These methods are also used for preparation for competition at altitude or for the acclimatization of mountaineers.

1. Traditional 'Live High-Train High' Altitude Training

Traditional altitude camps consist of living and training at moderate altitude (1800–2500 m) for several weeks, usually between 2 and 4 weeks. These LHTH camps are mostly carried out two to three times a year.

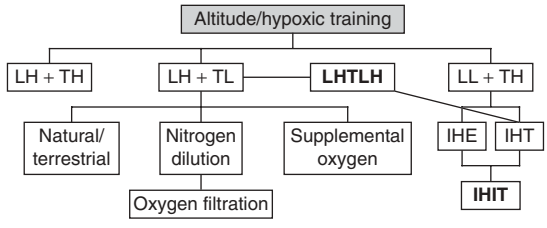

Fig. 1. Different hypoxic methods (modified from Wilber[1]). **IHE** = intermittent hypoxic exposure during rest; **IHT** = intermittent hypoxic training; **IHIT** = intermittent hypoxic exposure during interval training; **LH** = live high; **LHTLH** = live high-train low and high; **LL** = live low; **TH** = train high; **TL** = train low.

1.1 Different Phases

These LHTH camps consist of several progressive phases: the acclimatization phase, the primary training phase, the recovery and preparation for return to sea-level phase, and the return to sea level.

1.1.1 Acclimatization Phase

The first phase starts immediately on arrival to altitude and is called the acclimatization phase. As the name indicates, the purpose of this phase is to acclimatize the athletes to the reduced P_IO_2 (partial pressure of inspired oxygen) at altitude. To facilitate the athletes' acclimatization to altitude, they are exposed to as much open air activity as possible. This phase is the most critical one. Therefore, high-intensity exercise is not recommended. The athletes have to be advised to increase their recovery and their fluid intake. The acclimatization phase usually lasts 7–10 days, depending on the total duration of the LHTH camp and the athlete's frequency of hypoxic exposure, with the duration of exposure usually being decreased in athletes who have experienced regular exposure to altitude.[2]

1.1.2 Primary Training Phase

The primary training phase follows after the acclimatization phase. This phase lasts between 2 and 3 weeks, but may be prolonged according to the age, experience and goals for functional adaptation of the athletes. The purpose of this phase is to progressively increase training volume up to levels similar to those that are achieved at sea level, but also to progressively increase the intensity of training. Large workloads are necessary to induce the cumulative and residual effects of altitude training.[2] However, many athletes use shorter repetitions to maximize the speed aspect of training, or use the same work intervals that they carry out in training in normoxia whilst

increasing their recovery by a factor of 2–3. This area requires further scientific studies.

1.1.3 Recovery and Preparation for Return to Sea Level

This recovery phase lasts 2–5 days. The aim of this phase is to recover completely from the complementary altitude-induced fatigue. During this phase, training volume and intensity are gradually reduced.

1.1.4 Return to Sea Level

On return to sea level after an altitude training camp, three phases have been observed by coaches (figure 2). So far, however, these are not fully supported by the scientific evidence and are therefore under debate:

(i) A positive phase observed during the first 2–4 days, but not in all athletes.
(ii) A phase of progressive reestablishment of sea-level training volume and intensity. The probability of good performance is reduced.
(iii) 15–21 days after return to sea level, a third phase is characterized by a plateau in fitness. The optimal delay for competition is during this third phase, although some athletes reach their peak performance during the first phase.[3]

The time course of the different physiological factors that explain these post-altitude phases has not been studied and therefore remains unclear. However, one may postulate that the immediate positive effects (phase 1) are primarily due to the haemodilution resulting from the return to sea level and persistence of the ventilatory adaptations to altitude training. The decrease in performance fitness (phase 2) might be related to the altered energy cost and loss of the neuromuscular adaptations induced by training at altitude. Improvement in the latter factors after several days at sea level, in conjunction with the further increase in O_2 transport and delayed hypoxic ventilatory responses (HVRs) benefits, may explain the third positive phase. In addition, some benefits coming from the increased training capability that is directly induced by altitude training may lead to a delayed period (up to 6–7 weeks after finishing the altitude camp) of increased fitness.[2] In any case, the post-training period requires further scientific investigation.

1.2 Altitude Training Sites

Several altitude training sites exist around the world. The most famous within the sporting

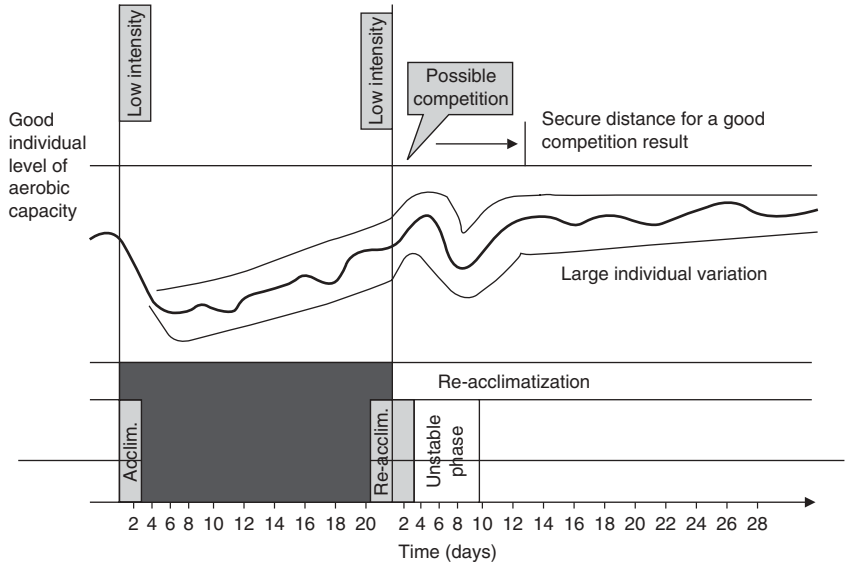

Fig. 2. Schematic view of the development of the aerobic capacity during and after 'live-high train-high' (LHTH) training (adapted from Fuchs and Reiss[3]). **Acclim.** = acclimatization.

community are (by ascending altitude; see Wilber[4] for a comprehensive review): Prémanon (1200 m, France); Thredbo (1350 m, Australia); Crans-Montana (1500 m, Switzerland); Albuquerque (1500 m, USA); Potchefstroom (1550 m, South-Africa); Snowfarm (1560 m, New Zealand); Pretoria (1750 m, South Africa); Boulder (1780 m, USA); Ifrane (1820 m, Morocco); St. Moritz (1820 m, Switzerland); Font-Romeu (1850 m, France); Colorado Springs (1860 m, USA); Kunming (1860 m, China); Belmeken (2000 m, Bulgaria); Eldoret (2100 m, Kenya); Flagstaff (2130 m, USA); Sierra Nevada (2320 m, Spain); Iten (2350 m, Kenya); Addis Ababa (2400 m, Ethiopia); Bogota (2640 m, Colombia); Quito (2740 m, Ecuador); La Paz (3600 m, Bolivia). These sites can offer relatively comfortable living and training conditions to athletes and coaches of all performance levels.

The first investigations into LHTH appeared during the mid-1960s. Since the 1990s, the LHTH method has largely been complemented by the other hypoxic methods.

2. Live High-Train Low (LHTL)

The traditional LHTH altitude training strategy has been replaced or complemented by the LHTL method.[1,5,6] The LHTL method was developed to invoke the beneficial effects of altitude (as regards cardiovascular, respiratory and metabolic adaptations) whilst avoiding, firstly, the need for a decrease in training intensity and, secondly, the detrimental effects of chronic hypoxia (such as muscular mass loss, fatigue or deteriorated aerobic performance, that are observed to a greater extent in endurance elite athletes subject to a more pronounced hypoxaemia[7]).

Levine's research team first investigated the LHTL methods by transporting the athletes from sea level or low altitude (<1300 m) to train whilst spending the rest of their time, i.e. living and sleeping at moderate altitude (1800–2500 m).[8] This method involved living at moderate altitude and performing low-intensity training at moderate altitude, and high-intensity training at sea level or lower altitude.[9] However, this method placed a large amount of stress and fatigue on the athletes as a result of descending from and ascending to altitude, travelling to and from training sites, adapting to weather differences between altitude and sea level, financial costs, etc.

The technical development of new devices made it possible to use artificial altitude (i.e. normobaric hypoxia via nitrogen dilution or oxygen extraction, altitude tents and/or hypoxic sleeping units, decompression chambers, or supplemental oxygen[4]) as an additional training stimulus without travelling to the mountains.

2.1 Haematological Adaptations

Levine et al.[8] found that levels of erythropoietin (EPO) were almost doubled, and haemoglobin concentration (Hb) was increased, in elite athletes after 27 days of living at 2500 m and training at 1250 m. In addition, Stray-Gundersen et al.[10] investigated the effects of 27 days of living at moderate altitude of 2500 m, training intensively at 1250 m, and undergoing base training at both 1250 and 3000 m. They observed a 92% increase in EPO within the first 20 hours of exposure. This was followed by a progressive decline in EPO, up to the 19th day, to the (initial) sea-level values. Moreover, after the 27 days of LHTL, Hb, haematocrit (Hct) and arterial O_2 saturation (S_aO_2) were increased. Dehnert et al.[11] investigated the haematological acclimatization to intensive training at low altitude (800 m) and spending13 h/day at moderate altitude (1960 m) in 15 male and six female triathletes over a period of 2 weeks. EPO increased significantly (30%) but temporarily in LHTL. Total Hb was unchanged in the LHTL group but showed a small significant decrease in the control sea-level group. Reticulocyte (Ret) count also showed a tendency to increase in the LHTL group, but was unchanged in the control group. The authors suggested that the observed EPO stimulation at altitude served to compensate for the exercise-induced destruction of red blood cells (RBCs). Moreover, Stray-Gundersen et al.[12] reported that, for elite athletes living at 2500 m and performing high-intensity training at 1250 m, EPO was almost doubled and both soluble transferrin receptor level and Hb were

increased. In contrast, Hahn et al.[13] evaluated the effects of LHTL (i.e. 8–11 h a night over 11–23 nights at 2650–3000 m) in six different studies with several athletic populations (runners, triathletes, kayakers, cyclists and cross-country skiers). They concluded that the increase in serum EPO (sEPO) did not always induce an increase in Ret production and that the other haematological parameters were not significantly different between the LHTL and control groups.

The Finnish research group, led by Rusko, reported important increases in EPO, Ret or RBCs with LHTL methods in elite athletes. Unfortunately, the training characteristics of their studies, which often lacked control groups, were sometimes poorly controlled. In six female elite cross-country skiers, living 14 h/day at a simulated altitude of 2500 m, and living and training at sea level for 10 h/day, a significant increase over the initial sea-level values was observed in both sEPO (31%) and Ret count (5%) after 11 days.[14] However, no sea-level control group was included in the study. Laitinen et al.[15] observed in seven male trained runners who lived 16–18 h/day at a simulated altitude of 2500 m and lived and trained the other 6–8 h/day at sea level, sEPO (84%) and RBC mass (7%) to be significantly increased (by 84% and 7% ,respectively) after 15 days of LHTL, and remain unchanged in the sea-level control group. Rusko et al.[16] demonstrated a 60% increase in sEPO when measured on the second day of LHTL in 12 female and male cross-country skiers and triathletes who lived 12–16 h/day for 25 days at a simulated altitude of 2500 m, and trained at sea level. They also noted a 5% increase in RBC mass following the 25 days of LHTL. However, the increase in sEPO was not correlated to the increase in RBC mass. The same research team[17] also recorded significant increases in sEPO, RBC, 2,3-diphosphoglycerate. Ret count and soluble transferrin receptors in ten healthy subjects who lived 12 h/day in a 15.4% O_2 (~2500 m) nitrogen room over a period of 7 days. Thus, 12 h/day of moderate normobaric hypoxia, for 1 week, was sufficient to stimulate erythropoiesis. Moreover, Phiel-Aulin et al.[18] evaluated six endurance athletes who completed 10 days of living 12 h/day at a simulated altitude of 2000 m whilst living and training for the rest of the day at sea level. After 2 days of LHTL, an increase was observed in sEPO (80%) and Ret count (60%). In addition, 1 week after the end of the LHTL period, measurements indicated that Hb (–2%) and Hct (–3%) were slightly decreased from the initial sea-level values. These post-LHTL decreases in Hb and Hct were attributed to haemodilution. Thus, a 10-day period of LHTL training induced a significant increase in sEPO but did not significantly change post-LHTL Hb or Hct in trained endurance athletes. The same authors[18] investigated the same 10-day LHTL period (i.e. 12 h/day living at 2700 m, and 12 h/day living and training at sea level) but at a higher simulated altitude of 2700 m in nine endurance athletes. Within the initial five days of LHTL a significant increase in sEPO (85%) and Ret count (38%) was observed. One week after the end of the LHTL period, higher Hb (3%) and lower Hct (–4%) values, compared with initial sea-level values, were observed. In contrast, the Australian Institute of Sport scientists observed very little haematological change with the LHTL method: i.e. no changes in any of the following measured haematological variables, % Ret, mean corpuscular Hb, reticulocyte Hb and total Hb mass, in six female road cyclists who slept for 12 nights at a simulated altitude of 2650 m and trained at 600 m above sea level.[19] They also studied, in six male middle distance runners, the effects of three 8-day LHTL periods (involving five 8- to 11-hour nights at a simulated altitude of 2650 m and training at 600 m, followed by 3 days of living and training at 600 m).[20] sEPO was increased in the LHTL group after the first (57%) and the fifth night (42%) of the first period but this increase was not as great in the second (13% and –4%) and third (26% and 14%) periods. Moreover, there were no changes in the other haematological variables. It appears, therefore, that 5 nights at 2650 m increased sEPO, but was insufficient to induce any other haematological changes. This hypoxic-induced sEPO response was down-regulated during a hypoxic stimulus.

The same Australian team[21] investigated the effects of an increased LHTL hypoxic stimulus,

i.e. a higher altitude (3000 m) over a longer period of time (23 days of 8–10 hours per night) in six male endurance athletes. No significant changes were observed in any of the measured variables. Recently, the same team reported that a much longer LHTL period (i.e. 46 nights of 9 hours per night at a simulated altitude of 2860 m, coupled with training at 600 m) induced a significant (~5.0%) increase in total Hb mass.[22] These results support the principle that the hypoxic dose is the primary factor leading to the observed haematological benefits resulting from LHTL.

Recently, a project funded by the IOC in Prémanon (in the Jura region of France) investigated the effects of various hypoxic training methods and more specifically the LHTL method.[23-34] These studies evaluated the responses to LHTL (i.e. 13–18 days of sleeping high at 2500–3500 m and training low at 1200 m) in cross-country skiers,[23,25,27,33] swimmers[24-26,28,29,31-33] and distance runners.[25,29,30,33,34] Overall, LHTL was well tolerated[23,29,33] for altitude up to 3000 m. These studies highlighted the benefits of monitoring sleeping S_aO_2 since oxygen desaturation and progressive re-saturation can be a good index of the degree of acclimatization. In line with the Scandinavian findings mentioned above[14-18] and summarized by Rusko et al.[35] in 2003, this set of studies support the principle of a minimum dose of hypoxia (of at least 14 hours, ideally 18 h/day) – at an altitude of at least 2500 m – and, ideally, 3000 m – for 3 weeks, being required to induce increased erythropoiesis. In fact, the runners who stayed for the longest time (18 days, 14 h/day) at 3000 m evidenced greater increases in Hb.[34] All the parameters except indirect markers of submaximal performance (see later) had returned to the baseline values 2 weeks after the LHTL session.

In summary, whereas some studies demonstrated significantly increased EPO and Ret count,[13-15,35-37] other studies did not observe either any or too low an erythropoietic effect to induce haematological changes after LHTL normobaric hypoxic exposure.[18-21] Probably the differences in duration and level of the hypoxic exposure, in training content or in the methods of measurement of blood volume parameters that were used (e.g. Evans blue dye vs CO rebreathing) play a role in the observed discrepancies. Only an absolute increase in RBC mass or Hb mass can be seen as an effective haematological benefit induced by altitude training. Unfortunately, many studies still report relative value(s) in terms of RBCs, Hb and Hct – all of which are influenced by change in volaemia. It was reported that the mean error of measurement for Hb mass with the CO-rebreathing method is 2.2% (90% CI 1.4, 3.5) since the error of measurement of the volume of RBCs is 2.8% (90% CI 2.4, 3.2) for the 51 chromium-labelled RBC technique, 6.7% (90% CI 4.9, 9.4) for the Evans blue dye technique and 6.7% (90% CI 3.4, 14) with the CO-rebreathing method.[38] These errors include analytical error, day-to-day biological variation and the interindividual variability in response to altitude training, and have direct implications for the monitoring of the athletes. Therefore, comparisons of values for RBC mass, plasma or RBC volume that have been obtained via different methods is unsatisfactory. Moreover, a large variation in RBC volume reported in previous LHTL studies[9,39] might arise from measurement errors obtained with the Evans blue dye method.[38]

Another confounding factor is the level of the subjects, i.e. trained versus elite athletes. It is known that endurance training induces an increase in blood volume. Heinicke et al.,[40] for example, reported that in elite endurance athletes, Hb mass and blood volume were ~35% higher, but Hb was no different, from the values observed in sedentary subjects. In contrast, acute altitude exposure has long been known to decrease (plasma) blood volume.[41] However, by comparing untrained subjects or elite cyclists native to either sea level or altitude (~2600 m), Schmidt et al.[42] showed that chronic altitude has a synergistic effect on blood volume parameters. Both Hb mass (for which the observed values were [mean ± SD] 17.1 ± 1.4 for cyclists native to altitude; 15.4 ± 0.9 for cyclists native to sea level; 13.4 ± 0.9 for sedentary individuals from altitude and 11.1 ± 1.1 g/kg for sedentary individuals native to sea level) and blood volume (for which the corresponding values were 116 ± 11; 107 ± 6; 88 ± 5 and 78 ± 8 mL/kg, respectively) were

affected both by altitude and, to a greater extent, by training. To conclude, differences in the level of ability and or training of the study subjects, as well as differences in their responses to both altitude and to training, make it very difficult to compare the haematological benefits of different hypoxic protocols across studies.

2.2 Non-Haematological Adaptations

Whether increased RBC volume is the primary factor that is responsible for the altitude-induced improvement in performance has recently been the subject of great debate.[43,44] It was noted that the change in performance is not necessarily associated with an increase in $\dot{V}O_{2max,}$ especially in elite athletes, and that the 86% variance in $\dot{V}O_{2max}$ could be attributed to factors other than change in RBC volume.[45] Two main peripheral factors have been proposed, as outlined below.

2.2.1 Economy

Several research groups have demonstrated 3–10% improvements in exercise economy[25,45-48] with altitude training. This might come from a decreased cost of ventilation, greater carbohydrate (CHO) use for phosphorylation, or, more likely, from improved mitochondrial efficiency (as denoted by P/O ratio or an increase in ATP production per mole of oxygen used).

2.2.2 pH Regulation and Muscle Buffer Capacity

The altitude-induced increase in the co-transport of lactate is related to the increase in the content of the relevant transporters (i.e. monocarboxylate MCT1 and MCT4). This allows for better lactate exchange and removal and, consequently, a slower pH decrease within 'glycolyic' exercise.[49] In addition, it is known that altitude acclimatization induces an increase in isoforms of carbonic anhydrase (CA) that influence both H^+ and HCO_3^- regulation.[50] These adaptive responses to altitude are likely to improve muscle buffering capacity, as reported previously,[45,48,51] and have been postulated to be, therefore, important in the explanation of post-altitude improvement in performance.[45,48] Whether this is actually the case is debatable. It was shown recently that acidosis (reduced pH) of muscles, is not a primary factor in the development of muscular fatigue. At physiological temperatures, acidification has a small effect on force production, shortening speed, the rate of glycolyic enzyme reactions or on the contractile process.[52] Moreover, acidification seems to preserve the muscle excitability.[53] It is beyond the scope of this review to discuss the main factors (i.e. inorganic phosphate) of muscle fatigue, but since the relationship between acidosis and fatigue is questioned, so is the direct influence of muscle buffering on performance. This is supported by the results of Gore et al.[48] that demonstrated no change in the total work performed during a 2-minute 'all-out' cycling trial despite an 18% increase in muscle buffer capacity. However, it is likely that the increased muscle buffer capacity observed after altitude training[51] is of high interest in high-intensity intermittent exercises.

2.3 Performance

Overall the improvement in performance that is obtained with LHTL has been evaluated as 1.0–1.5% for events lasting between 45 seconds and 17 minutes.[6,45]

Presenting altitude-induced change in performance or biological variables does not always provide information that is relevant for the practitioner (athlete, coach). As stated in Batterham and Hopkins,[54] "a non significant result ($p > 0.05$) effect does not necessary imply that there is no worthwhile effect." The smallest worthwhile effect on performance across a range of sports known for using altitude training (track and field, swimming, cycling) has been shown to be ±1%.[55-57] Since the biological variables presented in this review have a direct influence on performance (e.g. haemoglobin mass, RBC mass, economy or $\dot{V}O_{2max}$), one may also assume that ±1% is a correct approximation for their smallest worthwhile effect. It is also important to note that the effectiveness of an altitude training regimen is customarily expressed by the 'additional benefits' that are obtained over compared periods when similar training is conducted at sea level. Therefore, a given percentage increase has little practical significance *per se*.

2.3.1 Aerobic Performance

Levine et al.[8] reported, for 14 elite men and 8 elite women, that sea-level endurance performance was significantly increased after 27 days of living at 2500 m and training at 1250 m. This performance increment amounted to a 1.1% enhancement in 3000 m run-time trial time, and a 3% increase in $\dot{V}O_{2max}$. Thus, even elite athletes improved their sea-level performance after 27 days of LHTL strategy. Indeed, 6 years later, Levine and Stray-Gundersen[9] showed that 4 weeks of living at moderate altitude (2500 m) and training at low altitude (1250 m) improved sea-level performance more than equivalent sea-level or LHTH training in 13 well-trained runners. 5000 m run-time trial time was only significantly improved over the initial sea-level value (by an average of 13 ± 10 seconds 3 days after return to sea level) in the LHTL group. Velocity at $\dot{V}O_{2max}$ and the ventilatory threshold (VT) were also only improved in the LHTL condition. In addition, performance in the 5000 m run-time trial was similar 7, 14 and 21 days post-altitude, suggesting that the beneficial effects of LHTL may last for up to 3 weeks post-altitude. In contrast, the sea-level control group did not improve their 5000 m run performance at any time after completion of the 28-day training period.

The effectiveness of the LHTL method was confirmed later by the same research group who noted a 1.1–1.2% increase in sea-level 3000 m run time.[39] This improvement was accompanied by a 3% improvement in $\dot{V}O_{2max}$. The same group concluded that 4 weeks of acclimatization to moderate altitude, accompanied by high-intensity training at low altitude, improved sea-level endurance performance even in elite runners. In contrast, Hahn et al.[13] analysed six different LHTL studies and reported no significant increase in performance and even a tendency towards a decrease in $\dot{V}O_{2max}$. This tendency can be explained partly by the fact that Hb did not increase (see haematological adaptations) and that athletes with a high $\dot{V}O_{2max}$ at sea level probably regress to a large extent during altitude training[58] due to the loss of skeletal muscle mitochondria, and reduced oxidative enzyme activity[59,60] caused by the hypoxic stimulus. Therefore, apparently, mitochondrial alteration can occur at moderate altitudes (2650–3000 m) during a LHTL protocol. It is well known that for trained athletes, endurance performance may be independent of $\dot{V}O_{2max}$ and that other submaximal and/or non-haematological variables may have a great influence on their performance.[45,61]

In the study of Rusko et al.,[16] 1% and 3% increases in sea-level $\dot{V}O_{2max}$ at day 1 and 7 after the end of the LHTL period were observed. The latter authors concluded that living at a simulated altitude of 2500 m for 25 days significantly increased sea-level $\dot{V}O_{2max}$ approximately 1 week after the LHTL period. The same group[37] observed a 4% improvement in 40 km time trial performance on the fifth day following an 11-day LHTL period of living 14 hours a day at a simulated altitude of 2500 m. Since they did not include a control group in their study, it is difficult to know whether this performance enhancement was not primarily training induced.

In six male endurance athletes, after sleeping for 23 nights at a simulated altitude of 3000 m and training at 600 m, both a 4% decrease in $\dot{V}O_2$ at different submaximal intensities and a 1% increase in mechanical efficiency were reported.[48] In five elite female cyclists who performed LHTL (12 hours at 2650 m, 12 hours at 600 m) over 12 days, the mean power output during a 4-minute cycling time trial was increased to a greater extent (2.3%) in the LHTL group than in the control group (0.1%). In contrast, the mean power output during a 30-minute time trial was decreased in the LHTL group (−1.1%) but increased by 2.4% in the control group.[62] Moreover, Saunders et al.[46] observed a 3.3% decrease in $\dot{V}O_2$ averaged across three submaximal running speeds (14, 16 and 18 km/h) after 20 days of LHTL at 2000–3100 m and 600 m in elite distance runners. In addition, 5, 10 and 15 days of LHTL (8–10 hours at 2650 m and training at 600 m) in 19 well-trained cyclists did not induce any change in performance-related variables.[63] Saunders et al.[46] consequently suggested that 10 or 15 days of LHTL are not more effective than 5 days. In contrast, when combining all the data, i.e. 5, 10 and 15 days of LHTL, a 4% increase in mean power output during a 4-minute time trial over initial values was noticed after LHTL,

whereas no changes were shown in the sea-level control group. Nor was any change in sea-level $\dot{V}O_{2max}$ observed after 10 days of LHTL (12 h/day at 2700 m and training at sea level) in nine endurance athletes.[18]

Four groups had 4 weeks of 'high-high-low' training camp where they lived at 1780 m, 2085 m, 2454 m or 2805 m and trained together at low to moderate altitude (high-intensity workouts 1250–1780 m; base training 1700–3000 m). $\dot{V}O_{2max}$ increased after 4 weeks only at the three highest altitude exposures by 8 ± 85 mL, 206 ± 60 mL, 308 ± 60 mL, and 301 ± 73 mL respectively, with 2085 m and 2454 m statistically greater than 1780 m. Both of the groups living at 2085 m and 2454 m improved their 3000 m time by 2.8 ± 0.7% and 2.7 ± 0.6%, respectively; or 15.7 ± 4.0 and 16.6 ± 4.2 seconds, respectively ($p = 0.003$ and 0.002). The groups living at 1780 m and 2805 m did not improve these times (1.1 ± 0.05% and 1.4 ± 1.1%; 6.3 ± 3.1 and 9.0 ± 7.1 seconds, respectively).[64]

In the French multicentric project,[23-34] an increase in aerobic performance has been observed in some conditions, i.e. in swimmers[28] and runners,[34] but not in others, i.e. Nordic skiers.[27] The change in aerobic fitness and performance is determined by enhanced $\dot{V}O_{2max}$[34] or submaximal parameters.[25,28,34]

Overall, these findings show a greater increase in endurance performance with LHTL than with sea-level training, together with an improvement in mechanical efficiency and running economy in elite endurance athletes. LHTL seems to enhance performance to a greater extent in middle-distance aerobic exercise (i.e. lasting 4–10 min, such as the 4000 m team pursuit cycling event or 1500 m running) than in longer events (>30 min). However, few studies report no difference between LHTL and sea-level training.[13,27] Thus, the stress stimuli induced by the combination of training loads, recovery, hypoxic level and duration appear more important in terms of their influence on the ensuing physiological adaptations than those that are induced by hypoxia on its own.

2.3.2 Anaerobic Performance

Only a few investigations into the effects of LHTL on anaerobic performance have been conducted. Nummela and Rusko[65] observed a 1% improvement in 400 m race time in eight 400 m runners after a 10-day LHTL period (16–17 h/day at 2200 m and training at sea level), whereas no difference was observed in the control sea-level group. Moreover, the LHTL group ran significantly faster than the control group at 5.0 mmol/L blood La. The authors suggested that the improved 400 m sprint time after the LHTL period might have been due to an improvement in muscle buffer capacity. This was confirmed by Gore et al.'s[48] finding of a significant (18%) increase in skeletal muscle buffer capacity in six endurance athletes after 23 days of LHTL (sleeping at 3000 m and training at 600 m).

Hahn et al.[13] summarized several LHTL normobaric hypoxia studies and stated that sleeping in moderate normobaric hypoxia (2650–3000 m) for longer than 3 weeks could induce practical advantages for elite athletes, but that most of these potential benefits were not likely to result from haematological (i.e. increased Hb mass or increased $\dot{V}O_{2max}$) but, rather, from peripheral adaptations (i.e. muscle buffer capacity or mechanical efficiency).

The physiological adaptations are supposed to be identical when training in nitrogen-enriched or with oxygen-extracted hypoxia. However, the uncontrolled use of personal oxygen-extracted hypoxic devices (i.e. hypoxic tents) may lead to potential health problems that are not encountered in nitrogen-enriched equipment that is used under medical supervision. The preliminary studies[66,67] conducted on the Hypoxic Altitude Tent System™ (HAT) reported a large (16 ×) increase in CO_2 inside the HAT within the first hour of exposure at the simulated altitude of 2500 m. However, CO_2 did not reach unhealthy levels (>3.0%) and the athletes reported only small levels of discomfort or (adverse) side effects. These authors suggested that altitude tents provide a relatively safe and comfortable normobaric hypoxic environment.

2.4 LHTL: Summary and Proposals to Athletes

The *optimal altitude* for living high has been defined as 2200–2500 m to provide an optimal erythropoietic effect and up to 3100 m for

non-haematological parameters.[35,64,68,69] Owing to the flat shape of the oxy-haemoglobin dissociation curve above 60 mmHg, changes in P_aO_2 may not have much effect on S_aO_2. Indeed, P_aO_2 values below 60 mmHg are reached from altitudes of about 2500 m,[70] the optimal altitude for LHTH is therefore between 2200 and 2500 m.[71] It is well documented that 1800–1900 m is too low an altitude for inducing consistent and large increase in EPO.

The *optimal duration* at altitude appears to be 4 weeks for inducing accelerated erythropoiesis[9,68,69] whereas less than 3 weeks (i.e. 18 days) is long enough for beneficial changes in economy,[25,32,42,46] muscle buffering capacity,[45,48] the hypoxic ventilatory response[72] or Na^+/K^+ ATPase activity.[73,74]

One critical point is the *daily dose of altitude*. A natural altitude of 2500 m for 20–22 h/day (in fact, travelling down to the valley only for training) appears sufficient to increase erythropoiesis and improve sea-level performance.[9,46,69] 'Longer is better' as regards haematological changes, since additional benefits have been shown as hypoxic exposure increases beyond 16 h/day.[68] The minimum daily dose for stimulating erythropoiesis seems to be 12 h/day,[35] but larger benefits have been reported for exposure of 14–18 h/day.[28,34] For non-haematological changes, the implementation of a much shorter duration of exposure seems possible.

2.5 Advances in the LHTL Method: LHTLi, LHTL Interspersed

It is known that chronic hypoxia reduces muscle Na^+/K^+ ATPase content, whereas fatiguing contractions reduce Na^+/K^+ ATPase activity, both of which factors may impair performance.[74] One observed potential side effect of LHTL is the decrease in Na^+/K^+ ATPase activity that is detrimental to excitation-contraction coupling properties and, therefore, particularly relevant to high-intensity intermittent sports.[75] One way to reverse this detrimental effect is to alternate nights in hypoxia and nights in normoxia, for example, 5 nights in LHTL interspersed with 2 nights in normoxia.[73] This leads to an improved LHTL method that we call LHTLi (LHTL interspersed).

3. Intermittent Hypoxic Exposure

3.1 Definition

Intermittent hypoxic exposure (IHE) or periodic exposure to hypoxia is defined as an exposure to hypoxia lasting from seconds to hours that is repeated over several days to weeks. These intermittent hypoxic bouts are separated by a return to normoxia or lower levels of hypoxia.[76] IHE in combination with training sessions in hypoxia is referred to as intermittent hypoxic training (IHT).[4,6] Intermittent hypoxic interval training (IHIT) is defined as a method where during a single training session, there is alternation of hypoxia and normoxia. Several experimental designs with a great variability in the length of exposure (seconds to hours), the number of hypoxic exposures a day, the number of consecutive days of exposure, and the level of the hypoxic stimulus are used in endurance sport and have been studied.

IHE or IHT raise the question of the minimum duration of exposure for inducing erythropoiesis. Since only relative short periods of hypoxic stimulus are needed to stimulate EPO production,[77-81] it is assumed that IHE and IHT would be sufficient to induce significant increases in sEPO and RBCs and to consequently improve the endurance performance and $\dot{V}O_{2max}$, without all the negative effects of prolonged hypoxic exposure, such as fatigue, decrease in muscle mass or immunodepression.

3.2 Haematological Adaptations

After IHE in progressively increased hypobaric hypoxia (4000–5500 m) for 90 minutes three times a week for 3 weeks, Rodriguez et al.[78] reported a significant increase in Ret count (180%), RBCs (7%), Hb (13%) and Hct (6%). These authors showed that 90 minutes of passive hypoxic exposure was sufficient to obtain significant changes in haematological parameters. An interesting finding from their study was that blood viscosity was not increased. The S_aO_2 during hypoxia was

improved (from 60% to 78%). Unfortunately, no control group was included in the investigation.

In 16 male triathletes who were exposed 3 hours a day for 5 days a week over 4 weeks to a progressively increased simulated altitude (4000–5000 m), the same research group[82] observed significant 100% and 440% increases in sEPO 3 hours after the first and last IHE sessions, respectively. However, no significant changes were observed in the other haematological parameters (Ret, RBC, total plasma and serum transferrin receptors) that were monitored. The authors suggested that 180 minutes daily of IHE was sufficient to increase endogenous EPO secretion even in highly trained athletes but without producing the subsequent erythropoietic response. Therefore, it was unlikely that the performance would have been increased.

Their findings were confirmed by Ricart et al.,[83] who investigated the effects of IHE, i.e. 2 hours a day at a simulated altitude of 5000 m over 14 days, on resting and exercise responses in normoxia and hypoxia. After the IHE period, no changes were observed in any of the measured variables at rest or during a normoxic submaximal exercise. However, during a submaximal hypoxic exercise, ventilatory responses (VE from 55.5 to 67.7 L/min; tidal volume: from 2.0 to 2.6 L) and S_aO_2 (from 65% to 71%) significantly increased, showing the beginning of an acclimatization to altitude without any potential benefits for sea-level endurance performance. In addition, Frey et al.[84] observed no changes in haematological variables after a 21-day IHE period, 75 minutes a day at 6400 m ($F_IO_2 \approx$ 9%), in moderately trained athletes. Meanwhile, a significant increase in sEPO (38%) was measured 2 hours after the first IHE session.

Nevertheless, Hellemans[80] showed evidence that contradicted the results of previous IHE studies reporting an increase in EPO without any erythropoietic responses. He investigated the effects of a different IHE method that consisted of alternating 5 minutes of inhaling low O_2 gas mixture with 5 minutes of ambient air during 60 minutes. The protocol was two IHE sessions a day during 20 days in ten elite endurance athletes. The F_IO_2 was ~10% (5800 m) for the first 10 days and then ~9% (6400 m) for the last 10 days. Significant increases in Ret count (29%), Hb (4%) and Hct (5%) were reported.

3.3 Performance

The findings as regards the effect of IHE on endurance performance are equivocal:

Hellemans[80] reported a significant improvement (3%) in endurance performance. Rodriguez et al.[78] reported a significantly increased power output at the anaerobic threshold, but no significant changes in either $\dot{V}O_{2max}$ or cycling exercise time. Frey et al.[84] observed, after an IHE of 75 minutes a day at 6400 m ($F_IO_2 \approx$ 9%) over 21 days, no changes in submaximal or maximal exercise responses in moderately trained female and male athletes. Unfortunately, neither of these two studies included a non-IHE control group. In addition, Rodriguez et al.[85] divided 23 well-trained swimmers and runners to either a hypobaric hypoxic (IHE; simulated altitude of 4000–5500 m) or normoxic (control; 0–500 m) group. Both groups rested in a hypobaric chamber for 3 hours a day, 5 days a week over 4 weeks. No significant changes in time trial performance, i.e. 3000 m run or 100 m and 400 m swim, were observed, within or between groups. A significant increase in $\dot{V}O_{2max}$ (3.3% and 0.9%) and in ventilation at peak exercise (VE_{max}) [8.1% and 1.2%] in the IHE and control groups, respectively, was observed 3 weeks after the IHE period. However, no significant differences between groups were detected. Thus, IHE did not improve swimming or running performance in welltrained athletes to a greater extent than was observed in athletes who followed the same training programme without any hypoxic exposure.

In addition, Julian et al.[86] evaluated the effect of 4 weeks of IHE in seven elite distance runners. The IHE protocol was close to the one shown in Hellemans[80] and consisted of altering 5 minutes of hypoxic breathing with 5 minutes of normoxic ambient air over 70 minutes, five times a week. The F_IO_2 decreased progressively, from 12% in the first week to 11% in the second week and 10% in the third and fourth weeks. A sea-level control group, who followed the same protocol in normoxic conditions, was included. At days 1, 5, 10, and 19 of the IHE protocol and 10 and 25 days

after the IHE period, there were no significant differences in $\dot{V}O_{2max}$, 3000 m time trial performance, EPO, soluble transferrin receptor or reticulocyte parameters between groups. Thus, 4 weeks of IHE of 5:5 minutes hypoxic:normoxic exposure over 70 minutes five times a week did not induce any improvements in sea-level performance.

Recently the inefficiency of IHE has been demonstrated again in a double-blind study:[87] after 15 days of IHE (1 h/day of 6 minutes of breathing 10–11% O_2 gas mixture alternated with 4 minutes of breathing room air), neither the aerobic performance ($\dot{V}O_{2max}$) nor the anaerobic variables (peak or mean power during a Wingate test) differed from those of the control group.

Overall, in studies with control groups, IHE does not induce any substantial change in either haematological parameters or in endurance performance.

4. Intermittent Hypoxic Training (IHT)

Another way to benefit from hypoxic stimulus without undergoing the detrimental effects of a prolonged exposure to hypoxia is to train under hypoxic conditions and to remain at sea level for the rest of the time. Yet the living low training high (LLTH) approach, also called intermittent hypoxic training (IHT), may appear surprising since the time spent in hypoxia may not be sufficient to elicit a raise in RBCs like LHTL, and therefore improve O_2 carrying capacity. Furthermore, as during a long sojourn at altitude, the training velocity cannot be as high as at sea level because of the decrease in $\dot{V}O_{2max}$ with hypoxia.[88,89] However, LLTH could be advantageous anyway since it can induce an additional stimulus as compared with sea-level training. Specific molecular adaptations at muscular level have been reported after IHT unlike training in normoxia.[90] Over the last 20 years, many studies have reported interesting information about the effects of IHT at haematological and muscular levels and its consequences on performance. Roels et al.[61] also investigated the effects of a new simulated altitude strategy, i.e. IHIT, which is defined as a method whereby during a single training session, there is alternation of hypoxia and normoxia.

4.1 Haematological Adaptations

As expected, in view of the time required for erythropoiesis, no haematological change was reported by most of the studies after IHT. Three training sessions a week, each lasting 45 minutes to 1 hour, at simulated altitudes varying from 2500 to 4000 m over a period of 3–5 weeks did not induce a change in Hct or Hb.[91-93] According to several studies, an exposure of 1 h/day would be insufficient to elicit haematological changes.[93-96] Terrados et al.[97] have reported that even training sessions of 2 hours at 2300 m, repeated 4–5 times a week for 4 weeks, did not modify haematological parameters. These results are in agreement with the fact that several hours of continuous exposure to hypoxia are needed to obtain an increase in the levels of EPO.[79,98] These results were confirmed by Vallier et al.[91] in elite triathletes performing IHT 3 days a week over 3 weeks at a hypobaric-simulated altitude of 4000 m. The training sessions consisted of ~60 minutes of steady workouts at 66% of maximum power and interval workouts at 85% of maximum power. Seven days after the end of the IHT protocol, no significant differences were observed in the haematological variables.

However, IHT may be more efficient at improving haematological parameters if combined with IHE. Rodriguez et al.[77] examined the combined effects of IHE and IHT in 17 subjects who conducted a high-altitude expedition. IHE consisted in an exposure of 3–5 h/day for 9 days at altitudes that progressively increased (from 4000 m to 5500 m). In addition, the subjects had to perform three to five training sessions a week (30–75 minutes each) at low intensity. The authors observed a significantly increased RBC (+12%), Ret (+54%), Hb (+18%) and Hct (+11%) when the data of both groups were combined. These authors concluded that IHE in hypobaric hypoxia could stimulate the erythropoietic response. Casas et al.,[99] using the same protocol as Rodriguez et al.[77] but for 17 days, found significant increases in packed cell volume from 41% to 44.6%, in RBC from 4.61 to 4.97 10^6 cells/μL and in Hb from 14.8 to 16.4 g/dL. The authors suggested that short-term hypobaric hypoxia with

low-intensity training induced an improvement in the blood oxygen transport capacity.

To our knowledge, Meeuwsen et al.[100] are the only authors who reported an increase in Hct and Hb following a non-combined IHT. In their study, eight triathletes had to cycle for 2 h/day at 2500 m (60–70% of heart rate [HR] reserve) for 10 consecutive days. Two days after the IHT period, there was an increase in both Hct (48 ± 2% vs 43 ± 2%) and Hb (9.6 ± 0.19 vs 9.17 ± 0.27). Nevertheless, 9 days after the end of the training period these parameters had returned to their baseline values. According to the authors, this unexpected increase in both Hct and Hb cannot be explained by dehydration since there was no change in the plasma volume. On the other hand, it is possible that the concentration of training sessions over a 10-day period as well as their duration played a role in these haematological changes.

In view of all the results of the studies mentioned above, IHT alone does not seem to have any significant effect on haematological parameters. Combining this kind of training with IHE may, however, be efficient as a method of improving O_2 carrying capacity.

4.2 Muscular Adaptations

Training *per se* in hypoxia increases mitochondrial and capillary density, capillary-to-fibre ratio, fibre cross-section area, myoglobin content and oxidative enzyme activity such as citrate synthase.[101-104] Moreover, LLTH protocols improved $\dot{V}O_{2max}$ and endurance performance not only in hypoxic conditions but also at sea level.[97,101] Therefore, training under hypoxic conditions (~3850 m) seems to induce specific muscular and peripheral adaptations, due to activation of hypoxia-inducible factor 1α (HIF-1α), which is not activated to the same extent by training in normoxia or by passive hypoxic exposure.[90]

The study of Terrados et al.[102] is one of the first to have investigated the effects of IHT on muscle tissue in man. The protocol consisted of training one leg in normoxia and the other one in hypoxia (corresponding to 2300 m) for 30 minutes 3–4 times a week. Analysis of the muscular biopsies revealed that both citrate synthase activity and myoglobin content were higher after IHT as compared with sea-level training. Another study using a similar protocol confirmed that citrate synthase increased more after IHT (~3500 m; $F_IO_2 = 13.5\%$) than after training in normoxia.[101] On the other hand, Terrados et al.[102] did not report any change in citrate synthase after a 1-month IHT at ~2300 m in elite cyclists.

More recent studies have tested the effects of a 6-week IHT (five sessions/week) on muscular adaptations in untrained men.[90,105,106] The subjects were divided into normoxic and IHT (3850 m; $F_IO_2 = 13\%$) groups. Within each group, a high (at the anaerobic threshold) and a low (at ~25% below the anaerobic threshold) training intensity subgroup was formed. Muscle biopsies of the *vastus lateralis* showed an enhancement of capillary length density after IHT only, as well as a greater increase in mitochondrial volume density after IHT than after training at sea level. Interestingly, the greatest increases in both these parameters occurred in the IHT group who trained at high intensity. Thus, when IHT was performed at high intensity, it induced greater muscle adaptations to compensate for the decreased O_2 availability.

Together, these results demonstrate that IHT leads to muscular adaptations that either do not occur in normoxic conditions or, if they do so, do so to a lesser degree. These muscular changes may have an origin at the molecular level, via the activation of a transcription factor, namely HIF-1, expressed in skeletal muscle of all mammalians. Vogt et al.[90] have reported an increase in HIF-1α messenger RNA (mRNA) after both high (+ 82.4%) and low (+78.4%) training intensity in hypoxia (3850 m), demonstrating that IHT could modify the gene expression. The higher concentration of HIF-1α mRNA was accompanied by an increase in both mRNA of vascular endothelial growth factor (VEGF) and myoglobin but only after the high-intensity training in hypoxia. These findings made the authors conclude that training in hypoxia at high intensity is the most likely way to favour oxygen transport and utilization under hypoxic conditions.

Very recently, another study emphasized the role of exercising at high intensity on the extent

of muscular adaptations during IHT.[49,107] In this study, endurance-trained subjects performed 6 weeks of training at the second VT (VT_2). Contrary to the previous studies, training in hypoxia was not carried out at each session but included twice a week within the normal training of the athletes. Furthermore, the simulated altitude was lower (~2500 m). After the training period, most results of the muscular biopsies were significant. The authors especially found an increase in mRNA concentrations of HIF-1α (+104%), glucose transporter-4 (+32%), phosphofructokinase (+32%), citrate synthase (+28%), carbonic anhydrase-3 (+74%) or monocarboxylate transporter-1 (+44%). No change occurred in the control group. However, unlike what was previously reported,[78] there was no significant difference in mRNA concentrations of VEGF and myoglobin after IHT. The practical implications of the responses of the genes to training are still questionable.[108] Firstly, the observed increase in mRNA of these encoding proteins (enzymes, transcription factor) does not automatically induce an increase in the synthesis of the specific proteins regulating the response to altitude training. The continuity between specific signalling pathways and subsequent protein synthesis in response to altitude training has not been detailed. Secondly, there is a discrepancy between the local molecular changes and the global physiological changes, as shown for example in IHT by Vogt et al.[90] However, these results, by showing that the expression of many genes in muscles is specific to training in hypoxia and different to training in normoxia, highlight the complexity of the adaptive multifactorial response to altitude training.

4.3 Performance

The main objective of altitude training is to improve sea-level performance. Therefore, one could wonder whether the molecular and structural adaptations following IHT are advantageous after the return at sea level.

Since the LLTH method has been reported to improve some factors involved in O_2 utilization within the muscle[49,90,101,102,104,106,107] but also to positively modify pH regulation and lactate transport,[49] an improvement in aerobic and/or anaerobic performance might be expected after IHT.

4.3.1 Aerobic Performance

While several studies have reported that IHT induced a better aerobic performance in hypoxic conditions,[97,106,109] what about performance in a normoxic environment? Like the other hypoxic methods, the results are controversial.

Some studies did not find any change[91,97] or reported no greater improvement in normoxic $\dot{V}O_{2max}$ after LLTH than after sea-level training.[93,106] This result was confirmed by the studies of Roels et al.[61,110,111] IHIT and IHT of up to ~115 min/week were not sufficient to elicit a greater increase in aerobic performance or significant changes in haematological variables compared with a similar normoxic interval training.[61] However, these different training methods induced different responses during the 3-week post-training period: only the IHT group maintained their performance.

An IHT of ~380 min/week was not sufficient to elicit a greater increase in aerobic or anaerobic performances or significant changes in haematological variables and MCT1 and MCT4 protein content, when compared with a similar normoxic interval training. However, IHT improved the aerobic power at altitude.[110] An IHT of ~380 min/week altered the intrinsic properties of mitochondrial function, i.e. the substrate preference such that lower fat oxidation and increased glutamate utilization were observed.[111]

On the other hand, $\dot{V}O_{2max}$ increased 9 days after training in hypoxia in the study of Meeuwsen et al.,[100] whereas it was unchanged after 2 days. This may be explained by the higher concentration and duration of the training sessions. Nevertheless, a 5% increase in $\dot{V}O_{2max}$ has also been found by Dufour et al.[109] after 6 weeks of IHT in endurance trained runners. Furthermore, a dramatic improvement of the time to exhaustion (+35%) as well as a higher $\dot{V}O_2$ at VT_2 (+7%) was also reported in this study. According to the authors, these results were due to the combination of the hypoxic stimulus and the high training intensity that was established at VT_2. Another study using

high-intensity interval training (45–60 minutes within a 2-hour session in hypoxia) 4–5 times a week in elite cyclists reported an increase both in work capacity and in maximal power output during a laboratory test in normoxia.[97] It was concluded that performance at sea level was at least as much improved by hypoxic as by normoxic training.

Previously however, a 5-week high-intensity IHT did not lead to a greater improvement in $\dot{V}O_{2max}$ measured in normoxia in a 400 m freestyle than that obtained by sea-level training in swimmers.[92] Similar results concerning $\dot{V}O_{2max}$ as well as lactate threshold were reported in team sports players after a 4-week period of IHT that consisted of cycling 30 minutes at high intensity three times a week. In both these studies, the duration of the high-intensity exercises in hypoxia was shorter than in the study of Dufour et al.[109] (30 seconds to 1 minute vs 12–20 minutes) or Terrados et al.,[97] which could partly explain the lack of significant results. Recently, Roels et al.[110] have found that 3 weeks of IHT combining continuous training at low intensity (60% $\dot{V}O_{2max}$ three times a week) and interval training (100% of peak power output twice a week) had no effect on $\dot{V}O_{2max}$ and did not increase maximal power output more than training at sea level.

Another way to perform IHT is to use interval exercises alternating hypoxia and normoxia periods (IHIT). This original approach does, however, not seem efficient in eliciting a greater increase in aerobic performance or significant changes in haematological variables compared with similar normoxic interval training.[61] Another strategy could be to combine IHE and IHT within the same training period. Using this approach, Rodriguez et al.[77] found a significant increase in exercise time (+3.9%) and VE_{max} (+5.5%) but without any change in $\dot{V}O_{2max}$. These authors suggested that short-term IHE stimulates EPO secretion (see haematological adaptations), which in turn enhances endurance performance. The same research group[99] also reported that the combination of IHT and IHE induced a decrease in submaximal HR, a shift to the right of the lactate versus exercise load curve, and an increase in the anaerobic threshold, which indicates an enhanced endurance performance.

When taking into account the results of all the studies presented above, one could conclude that IHT might have a positive impact on aerobic performance but whether it does so or not probably depends on the combination of exercise duration and intensity as well as on the degree of hypoxia during training.

4.3.2 Anaerobic Performance

Very few studies have, to date, focused on the effects of IHT on anaerobic performance. Among these studies only one has found positive effects.[100] In this study, 9 days after training in hypoxia, performance in the Wingate test (i.e. an anaerobic specific test) significantly increased, in contrast to what was observed in the control group. Both peak and mean power reached during this test were improved, by about 5% on average. Furthermore, the time to peak was decreased by 37%. Another study also found an improvement in peak and mean power during the Wingate test but the difference was not significant compared with the group who trained at sea level.[112] Truijens et al.,[92] who assessed anaerobic performance in swimmers using a 100 m freestyle time trial, did not find a greater improvement in the hypoxic than in the control group. They also reported no change in anaerobic capacity, as assessed by the accumulated oxygen deficit.

The current data are probably insufficient to conclude whether IHT has a positive impact on anaerobic performance or not. Even though some factors involved in pH regulation or lactate transportation could change after IHT[49] and could therefore be advantageous for anaerobic glycolysis, further studies will have to be carried out to provide more information.

4.4 An Original Intermittent Hypoxic Training (IHT) Method: Training with Voluntary Hypoventilation

Very recently, two studies have demonstrated that it could be possible to get a significant arterial desaturation during exercise without being placed in an hypoxic environment.[113,114] This is actually possible by voluntarily reducing the breathing frequency and by holding one's breath at low

pulmonary volumes. Thus, repeatedly using this respiratory technique during training would represent an intermittent hypoxic exposure and could therefore be likened to IHT, although hypoventilation also induces hypercapnia.

Woorons et al.[113] have shown that training that way did not modify haematological parameters or aerobic performance. On the other hand, the authors reported both a higher pH and HCO_3^- at a high submaximal intensity reflecting a delayed acidosis possibly due to an improvement in the buffer capacity. Furthermore, the velocity at maximal exercise was improved by 0.5 km/h in 85% of the subjects and correlated to the change in HCO_3^- at submaximal exercise. Even though no other study has ever investigated the effects of voluntary hypoventilation training, these first results suggest that this training method could be advantageous for anaerobic performance. Further studies should in any case bring more knowledge to bear on this specific topic.

4.5 IHT: Summary and Proposals to Athletes

Athletes engaged in endurance sports could take advantage of IHT especially during the precompetitive phase. Twice a week, they should include in their training programme a training session including 30–45 minutes of high-intensity exercises at a simulated altitude of 2500–3000 m. The high-intensity exercises should be around the anaerobic threshold and organized in series of 10–20 minutes. To obtain a greater improvement in aerobic capacity, in addition to IHT, athletes could spend 3 hours in hypoxia at rest, 4–5 times a week.

IHT seems more beneficial than IHE in performance enhancement, but without clear explanation. The results of Hoppeler and Vogt[115] are promising in that they show that hypoxic exercise intensity *per se* might play a role on adaptations at the molecular level in skeletal muscle tissue. While research on intermittent hypoxia has accelerated in the recent years, many basic and applied questions still remain to be answered.

Overall as pointed out by Wilber,[1] it is unlikely that IHT induces any improvement in $\dot{V}O_{2max}$ as a result of the altitude dose (no IHT studies have reported this increase). However, improvement in athletic performance is likely to happen with high intensity (above ventilatory threshold) due to an increase in mitochondrial efficiency and pH/lactate regulation.[49,107,116]

4.6 A Promising Combination: Living High-Training Low and High, Interspersed

There is an agreement that LHTL induces some slight increase in aerobic performance (1.0–1.5%)[1,117] and we propose using a modified pattern by alternating nights high and nights low (LHTLi; e.g. 5–2 or 6–1). In addition, there is clear evidence that intense exercise at high altitude stimulates to a greater extent the muscle adaptations for both aerobic and anaerobic exercise and limits the decrease in power.

It is currently unknown if coupling LHTL and ITH would be the optimal combination and further scientific investigations are required. However, we suggest that a training pattern associating LHTLi (five nights at 3000 m and two nights at sea level) with training at sea level except for a few (2.3 per week) sessions of suprathreshold training might be very efficient, especially in intermittent sports (football, tennis, squash). Of interest is that this combination of hypoxic methods (that we suggest naming LHTLHi) is currently used with success by squash and football players in a sports academy, and was used by a national football team during the qualification games for the 2010 World Cup.

5. Proposals for Optimal Combination of Hypoxic Methods in the Yearly Training Plan

One of the most difficult tasks of the coach is to lead his athletes at their peak fitness at the appropriate time, i.e. for the main competition. Periodization is critical in every sport and periodization of hypoxic training is very challenging.

As described in this review, the underlying mechanisms behind the effects of hypoxic training are widely debated. Although the popular view is that altitude training may lead to an increase in haematological capacity, this may not be the main, or the

a

Base model: combination between hypoxic training and normoxic training in the preparatory training period									
Hypoxia		■	■	■					
Normoxia					■	■	■	■	■
Training load	Very high						■	■	
	High			■			■	■	
	Medium		■	■		■	■	■	
	Low	■	■	■		■	■	■	
	Very low	■	■	■	■	■	■	■	■
Training Int		Int ≤ VT_1 strength training	Int ≤ VT_1 Int ≤ VT_2 strength training	Int ≤ VT_1 Int ≤ VT_2 Int ≤ MAP strength training	Int ≤ VT_1	Int ≤ VT_1 Int ≤ VT_2 strength training	Int ≤ VT_1 Int ≤ VT_2 Int ≤ MAP strength training	Int ≤ VT_1 Int ≤ VT_2 Int ≤ MAP strength training	Recovery int ≤ VT_1
Days		7	7	7	7	7	7	7	7

b

Hypoxic training model: to prepare a period of competitions at altitude									
Hypoxia		■	■	■			■	■	■
Normoxia					■	■			
Training load	Very high			■					■
	High			■					■
	Medium		■	■		■	■		■
	Low	■	■	■		■	■		■
	Very low	■	■	■	■	■	■	■	■
Training intensity		Int ≤ VT_1 strength training	Int ≤ VT_1 Int ≤ VT_2 strength training	Int ≤ VT_1 Int ≤ VT_2 Int ≤ MAP strength training	Int ≤ VT_1	Int ≤ VT_1 Int ≤ VT_2 strength training	Int ≤ VT_1 Int ≤ VT_2 Int ≤ MAP strength training	Short recovery Int ≤ VT_1	Competition period at altitude
Days		7	7	7	7	6	5	2 to 3	1 to 15

c

Hypoxic training model: to prepare a period of competitions at sea level									
Hypoxia		■	■	■					
Normoxia					■	■	■	■	■
Training load	Very high			■					■
	High			■			■		■
	Medium		■	■		■	■		■
	Low	■	■	■		■	■		■
	Very low	■	■	■	■	■	■	■	■
Training intensity		Int ≤ VT_1 strength training	Int ≤ VT_1 Int ≤ VT_2 strength training	Int ≤ VT_1 Int ≤ VT_2 Int ≤ MAP strength training	Int ≤ VT_1	Int ≤ VT_1 Int ≤ VT_2 strength training	Int ≤ VT_1 Int ≤ VT_2 Int ≤ MAP strength training	Short recovery Int ≤ VT_1	Competition period at sea level
Days		7	7	7	7	6	5	2 to 3	1 to 15

Fig. 3. Schematic view of combinations between periods of training in hypoxic and normoxic conditions: one to three base models can be proposed during the preparatory training period depending on the duration of this period: (**a**) base training; (**b**) preparation for competitions at altitude; and (**c**) preparation for competitions at sea level. A base training model can be followed by an hypoxic training model to prepare competitions at sea level or at altitude. **Int** = intensity of the training; **MAP** = maximal aerobic power; **VT_1** = first ventilatory threshold; **VT_2** = second ventilatory threshold.

only, factor involved in the improvement of performance. Other central (such as ventilatory, haemodynamics or neural adaptations) or peripheral (such as muscle-buffering capacity or economy) factors play an important role. Therefore, it is logical that the extent to which an athlete may benefit from

these different methods of hypoxic training will differ according to both his/her general and specific training focus (i.e. between endurance, intermittent such as team sports and racket sports, or sprint/power sports; and between different periods of the training year). To date, there is no study that has investigated how to incorporate hypoxic training into the athlete's general training programme. So the following proposal requires further investigation. We propose two different patterns of combination of hypoxic and normoxic methods.

The first proposal is a 'traditional' approach using only terrestrial LHTH hypoxic exposure and combines high-high and sea-level training phases during the base training (figure 3a), to prepare for a competition in altitude (figure 3b) and at sea level (figure 3c), respectively.

The second proposal combines all the hypoxic methods described in this review (LHTH, LHTL, LHTLHi and IHT) and therefore requires some specific technological equipment.

5.1 Combining High-High Hypoxic and Sea-Level Training

The choice of the duration, altitude level; i.e. altitude dose and training content; volume; intensity; i.e. training load is paramount in order to optimize the hypoxic benefits and to peak in elite athletes.

The intensity of training lower or equal to the first VT (VT_1) can be considered as the base of the training for the high-level athletes in endurance.[118-123] This intensity of training is particularly important in association with hypoxic stress, especially during the acute hypoxic period as shown by Schmitt et al.[24] Indeed, the acute hypoxic situation modifies autonomic nervous system (ANS) activity by decreasing the total

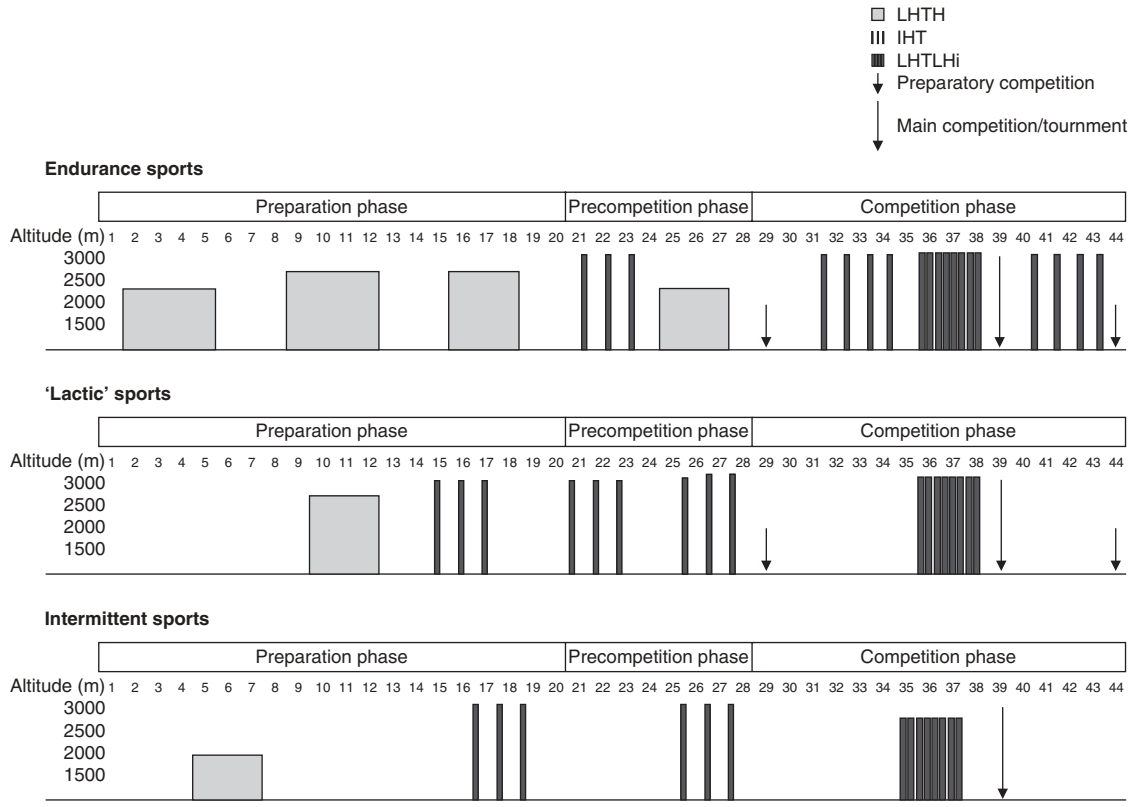

Fig. 4. Schematic view of periodization of hypoxic methods in endurance, glycolitic and intermittent sports. **IHT** = intermittent hypoxic training; **LHTH** = living high-training high; **LHTLHi** = living high-training low and high interspersed.

Table I. Overall efficiency of various hypoxic methods (calculated from Wilber[1])

Hypoxic method	Number of studies	Increased performance/positive mechanisms	No additional effect	Negative mechanisms
Nitrogen dilution	19	12	2	5
Oxygen filtration	10	5	2	3
LHTL		**58%**	**14%**	**28%**
IHT	16	8	8	0
		50%	**50%**	**0%**
All	45	56%	18%	18%

IHT = intermittent hypoxic training; **LHTL** = live high-train low.

heart rate variability (HRV) and especially high frequency activity (HF),[118] whereas training at or lower than VT_1 intensity increases HRV and HF.[124] Furthermore, Seiler et al.[121] showed that VT_1 may define 'binary' thresholds for ANS/HRV recovery in highly trained athletes. The association of training at an intensity lower or equal to VT_1 and hypoxic stress is thus well supported by athletes and is an optimal combination to improve aerobic capacities during the critical period of the acute hypoxia. Progressively after the acclimatization period, usually from the ~8th day, HRV and HF start to increase.[125] It is therefore possible to prescribe higher training intensities, for example, between VT_1 and the second ventilatory threshold (VT_2), and progressively intensities higher than VT_2.

5.2 Combining All Hypoxic Methods

The second proposal aims to use advanced technological methods in order to combine haematological and peripheral benefits of each of these methods in order to improve peak performance in elite athletes.

Periodization in three types of sports are proposed and summarized in figure 4.

5.2.1 Endurance Sports

Since extensive 'base training' is paramount in this type of sport, LHTH training during winter appears appropriate. The decline in exercise intensity will not be detrimental at this time of the year. Repeating several LHTH sojourns at high altitude will also help to speed up the acclimatization from one camp to another. It is known that the threshold altitude for a sustained increase in blood EPO concentration is about 2200 m. We therefore recommend two to three sojourns of 3–4 weeks each between 2200 and 2500 m.

During the pre-competition phase, a shorter sojourn (18–21 days) at a lower altitude (1800–2000 m) will allow more intense interval-training sessions.

During the competition period, athletes can benefit from intense IHT sessions or – if there is a break from a LHTLHi block (sleeping high at 3000 m for 5 days – sleeping at sea level for 2 days and training in normoxia except for two hypoxic 'threshold' sessions per week).

5.2.2 'Glycolytic' Sports

During the winter preparation, the programme would benefit from a sojourn at altitude (2200–2500 m) aiming to increase the RBC volume. Later, inclusion of 3-week blocks (1–2 IHT sessions per week: supramaximal interval training and/or lactate tolerance session at high altitude 3000 m) alternated with normoxic-only training would boost the muscle 'anaerobic' adaptations.

Prior to the main competition, LHTLHi (2–3 weeks of sleeping high 3000 m for 5 days – sleeping at sea level for 2 days and training in normoxia except for two hypoxic interval-training sessions per week) would allow peaking without reducing the intensity of the specific sessions.

5.2.3 Intermittent Sports

During phase 1 of the winter preparation, a sojourn at a low altitude (1500–1700 m) would be of benefit, aiming to develop aerobic fitness. Later, a few blocks of 3 consecutive weeks (1–2 IHT sessions per week: supramaximal interval training) would help to increase muscle adaptations for pH and buffer capacity.

LHTLHi (2–3 weeks of sleeping high at 2500 m for 5 days, sleeping at sea level for 2 days and training in normoxia except for one hypoxic interval-training session per week) would be appropriate to boost both central and peripheral adaptations prior to the main tournament/performance.

6. Conclusions

The aims and benefits of the various hypoxic methods are numerous and extend beyond an increase in O_2 transport capacity. It is known that IHE is inefficient for performance enhancement. The efficiency of the other methods was evaluated in a recent review[1] and is summarized in table I.

LHTL has been well investigated; the other methods (IHT and LHTLHi) still require further investigation to better understand their outcomes and mechanisms. However, the further development of practical expertise in hypoxic training will predominantly involve decisions about how to combine these methods in order to induce optimal performance in various types of sports and to reach peak performance in the athlete's main competitions.

Acknowledgements

No sources of funding were used to assist in the preparation of this article. The authors have no conflicts of interest that are directly relevant to the content of this article. The authors acknowledge the anonymous reviewers for their valuable comments and Dr V.E. Vleck who thoroughly reviewed the English manuscript.

References

1. Wilber RL. Application of altitude/hypoxic training by elite athletes. Med Sci Sports Exerc 2007 Sep; 39 (9): 1610-24
2. Issurin V. Altitude training: an up-to-date approach and implementation in practice. Sporto Mokslas 2007; 1 (47): 12-9
3. Fuchs U, Reiss M. Höhentraining: das Erfolgskonzept der Ausdauersportarten. Trainerbibliothek 1990; 27: 128
4. Wilber RL. Altitude training and athletic performance. Champaign (IL): Human Kinetics, 2004
5. Wilber RL. Current trends in altitude training. Sports Med 2001; 31 (4): 249-65
6. Hahn AG, Gore CJ. The effect of altitude on cycling performance: a challenge to traditional concepts. Sports Med 2001; 31 (7): 533-57
7. Mollard P, Woorons X, Letournel M, et al. Determinants of maximal oxygen uptake in moderate acute hypoxia in endurance athletes. Eur J Appl Physiol 2007 Aug; 100 (6): 663-73
8. Levine BD, Stray-Gundersen J, Duhaime G, et al. "Living high-training low": the effect of altitude acclimatization/normoxic training in trained runners [abstract]. Med Sci Sports Exerc 1991; 23: S25
9. Levine BD, Stray-Gundersen J. "Living high-training low": effect of moderate-altitude acclimatization with low-altitude training on performance. J Appl Physiol 1997 Jul; 83 (1): 102-12
10. Stray-Gundersen J, Chapman RF, Levine BD. HILO training improves performance in elite runners [abstract no. 198]. Med Sci Sports 1998; 30 (5): Suppl
11. Dehnert C, Hutler M, Liu Y, et al. Erythropoiesis and performance after two weeks of living high and training low in well trained triathletes. Int J Sports Med 2002 Nov; 23 (8): 561-6
12. Stray-Gundersen J, Chapman RF, Levine BD. "Living high-training low" altitude training improves sea level performance in male and female elite runners. J Appl Physiol 2001 Sep; 91 (3): 1113-20
13. Hahn AG, Gore CJ, Martin DT, et al. An evaluation of the concept of living at moderate altitude and training at sea level. Comp Biochem Physiol A Mol Integr Physiol 2001 Apr; 128 (4): 777-89
14. Rusko HK, Leppavuori A, Makela P. Living high-training low: a new approach to altitude training at sea level in athletes [abstract]. Med Sci Sports 1995; 27 Suppl. 5: S6
15. Laitinen H, Apolaeus K, Heikkinen R. Acclimatization to living in normobaric hypoxia and training at sea level in runners [abstract]. Med Sci Sports 1995; 27 Suppl. 5: S109
16. Rusko HK, Tikkanen H, Paavolainen L. Effect of living in hypoxia and training in normoxia on sea level V̇O2max and red cell mass [abstract]. Med Sci Sports 1999; 31 Suppl. 5: S86
17. Koistinen PO, Rusko H, Irjala K, et al. EPO, red cells, and serum transferrin receptor in continuous and intermittent hypoxia. Med Sci Sports Exerc 2000 Apr; 32 (4): 800-4
18. Phiel-Aulin K, Svedenhag J, Wide L. Short-term intermittent normobaric hypoxia: haematological, physiological and mental effects. Scand J Med Sci Sports 1998; 8: 132-7
19. Ashenden MJ, Gore CJ, Martin DT, et al. Effects of a 12-day "live high, train low" camp on reticulocyte production and haemoglobin mass in elite female road cyclists. Eur J Appl Physiol Occup Physiol 1999 Oct; 80 (5): 472-8
20. Ashenden MJ, Gore CJ, Dobson GP, et al. Simulated moderate altitude elevates serum erythropoietin but does not increase reticulocyte production in well-trained runners. Eur J Appl Physiol 2000 Mar; 81 (5): 428-35
21. Ashenden MJ, Gore CJ, Dobson GP, et al. "Live high, train low" does not change the total haemoglobin mass of male endurance athletes sleeping at a simulated altitude of 3000 m for 23 nights. Eur J Appl Physiol Occup Physiol 1999 Oct; 80 (5): 479-84
22. Saunders PU, Telford RD, Pyne DB, et al. Improved running economy and increased hemoglobin mass in elite

runners after extended moderate altitude exposure. J Sci Med Sport 2007 Dec 7

23. Tiollier E, Schmitt L, Burnat P, et al. Living high-training low altitude training: effects on mucosal immunity. Eur J Appl Physiol 2005 Jun; 94 (3): 298-304
24. Schmitt L, Hellard P, Millet GP, et al. Heart rate variability and performance at two different altitudes in well-trained swimmers. Int J Sports Med 2006 Mar; 27 (3): 226-31
25. Schmitt L, Millet G, Robach P, et al. Influence of ''living high-training low'' on aerobic performance and economy of work in elite athletes. Eur J Appl Physiol 2006 Jul; 97 (5): 627-36
26. Roels B, Hellard P, Schmitt L, et al. Is it more effective for highly trained swimmers to live and train at 1200 m than at 1850 m in terms of performance and haematological benefits? Br J Sports Med 2006 Feb; 40 (2): e4
27. Robach P, Schmitt L, Brugniaux JV, et al. Living high-training low: effect on erythropoiesis and maximal aerobic performance in elite Nordic skiers. Eur J Appl Physiol 2006 Aug; 97 (6): 695-705
28. Robach P, Schmitt L, Brugniaux JV, et al. Living high-training low: effect on erythropoiesis and aerobic performance in highly-trained swimmers. Eur J Appl Physiol 2006 Mar; 96 (4): 423-33
29. Povea C, Schmitt L, Brugniaux J, et al. Effects of intermittent hypoxia on heart rate variability during rest and exercise. High Alt Med Biol 2005 Fall; 6 (3): 215-25
30. Pialoux V, Mounier R, Ponsot E, et al. Effects of exercise and training in hypoxia on antioxidant/pro-oxidant balance. Eur J Clin Nutr 2006 Dec; 60 (12): 1345-54
31. Mounier R, Pialoux V, Cayre A, et al. Leukocyte's Hif-1 expression and training-induced erythropoietic response in swimmers. Med Sci Sports Exerc 2006 Aug; 38 (8): 1410-7
32. Cornolo J, Fouillot JP, Schmitt L, et al. Interactions between exposure to hypoxia and the training-induced autonomic adaptations in a ''live high-train low'' session. Eur J Appl Physiol 2006 Mar; 96 (4): 389-96
33. Brugniaux JV, Schmitt L, Robach P, et al. Living high-training low: tolerance and acclimatization in elite endurance athletes. Eur J Appl Physiol 2006 Jan; 96 (1): 66-77
34. Brugniaux JV, Schmitt L, Robach P, et al. Eighteen days of ''living high, training low'' stimulate erythropoiesis and enhance aerobic performance in elite middle-distance runners. J Appl Physiol 2006 Jan; 100 (1): 203-11
35. Rusko HK, Tikkanen HO, Peltonen JE. Oxygen manipulation as an ergogenic aid. Curr Sports Med Rep 2003 Aug; 2 (4): 233-8
36. Gore CJ, Gawthorn KM, Clark S. Does intermittent normobaric hypoxic exposure uncouple submaximal $\dot{V}O2$ and power [abstract]? Med Sci Sports 1999; 31 Suppl. 5: S190
37. Mattila V, Rusko HK. Effect of living high and training low on sea level performance in cyclists [abstract]. Med Sci Sports 1996; 28 Suppl. 5: S157
38. Gore CJ, Hopkins WG, Burge CM. Errors of measurement for blood volume parameters: a meta-analysis. J Appl Physiol 2005 Nov; 99 (5): 1745-58
39. Chapman RF, Stray-Gundersen J, Levine BD. Individual variation in response to altitude training. J Appl Physiol 1998 Oct; 85 (4): 1448-56
40. Heinicke K, Wolfarth B, Winchenbach P, et al. Blood volume and hemoglobin mass in elite athletes of different disciplines. Int J Sports Med 2001 Oct; 22 (7): 504-12
41. Myhre LG, Dill DB, Hall FG, et al. Blood volume changes during three-week residence at high altitude. Clin Chem 1970 Jan; 16 (1): 7-14
42. Schmidt W, Heinicke K, Rojas J, et al. Blood volume and hemoglobin mass in endurance athletes from moderate altitude. Med Sci Sports Exerc 2002 Dec; 34 (12): 1934-40
43. Gore CJ, Hopkins WG. Counterpoint: positive effects of intermittent hypoxia (live high: train low) on exercise performance are not mediated primarily by augmented red cell volume. J Appl Physiol 2005 Nov; 99 (5): 2055-7; discussion 7-8
44. Levine BD, Stray-Gundersen J. Point: positive effects of intermittent hypoxia (live high: train low) on exercise performance are mediated primarily by augmented red cell volume. J Appl Physiol 2005 Nov; 99 (5): 2053-5
45. Gore CJ, Clark SA, Saunders PU. Nonhematological mechanisms of improved sea-level performance after hypoxic exposure. Med Sci Sports Exerc 2007 Sep; 39 (9): 1600-9
46. Saunders PU, Telford RD, Pyne DB, et al. Improved running economy in elite runners after 20 days of simulated moderate-altitude exposure. J Appl Physiol 2004 Mar; 96 (3): 931-7
47. Neya M, Enoki T, Kumai Y, et al. The effects of nightly normobaric hypoxia and high intensity training under intermittent normobaric hypoxia on running economy and hemoglobin mass. J Appl Physiol 2007 Sep; 103 (3): 828-34
48. Gore CJ, Hahn AG, Aughey RJ, et al. Live high: train low increases muscle buffer capacity and submaximal cycling efficiency. Acta Physiol Scand 2001 Nov; 173 (3): 275-86
49. Zoll J, Ponsot E, Dufour S, et al. Exercise training in normobaric hypoxia in endurance runners. III: Muscular adjustments of selected gene transcripts. J Appl Physiol 2006 Apr; 100 (4): 1258-66
50. Juel C, Lundby C, Sander M, et al. Human skeletal muscle and erythrocyte proteins involved in acid-base homeostasis: adaptations to chronic hypoxia. J Physiol 2003 Apr 15; 548 (Pt 2): 639-48
51. Mizuno M, Juel C, Bro-Rasmussen T, et al. Limb skeletal muscle adaptation in athletes after training at altitude. J Appl Physiol 1990 Feb; 68 (2): 496-502
52. Westerblad H, Allen DG, Lannergren J. Muscle fatigue: lactic acid or inorganic phosphate the major cause? News Physiol Sci 2002 Feb; 17: 17-21
53. Pedersen TH, Nielsen OB, Lamb GD, et al. Intracellular acidosis enhances the excitability of working muscle. Science 2004 Aug 20; 305 (5687): 1144-7
54. Batterham AM, Hopkins WG. Making meaningful inferences about magnitudes. Int J Sports Physiol Perform 2006; 1: 50-7

55. Paton CD, Hopkins WG. Variation in performance of elite cyclists from race to race. Eur J Sport Sci 2006; 6: 1-7
56. Hopkins WG. Competitive performance of elite track-and-field athletes: variability and smallest worthwhile enhancements. Sportscience 2005; 9: 17-20
57. Pyne D, Trewin C, Hopkins W. Progression and variability of competitive performance of Olympic swimmers. J Sports Sci 2004 Jul; 22 (7): 613-20
58. Jensen K, Nielsen TS, Fiskestrand A, et al. High-altitude training does not increase maximal oxygen uptake or work capacity at sea level in rowers. Scand J Med Sci Sports 1993; 3: 256-62
59. Green HJ, Sutton JR, Cymerman A, et al. Operation Everest II: adaptations in human skeletal muscle. J Appl Physiol 1989 May; 66 (5): 2454-61
60. Hoppeler H, Kleinert E, Schlegel C, et al. Morphological adaptations of human skeletal muscle to chronic hypoxia. Int J Sports Med 1990 Feb; 11 Suppl. 1: S3-9
61. Roels B, Millet GP, Marcoux CJ, et al. Effects of hypoxic interval training on cycling performance. Med Sci Sports Exerc 2005 Jan; 37 (1): 138-46
62. Martin DT, Hahn AG, Lee H, et al. Effects of q 12-day "live high, train low" cycling camp on 4-min and 30-min performance. Med Sci Sports 2002; 34 Suppl. 5: S274
63. Roberts AD, Clark SA, Townsend NE, et al. Changes in performance, maximal oxygen uptake and maximal accumulated oxygen deficit after 5, 10, and 15 days of live high: train low altitude exposure. Eur J Appl Physiol 2003; 88: 390-5
64. Witkowski S, Karlsen T, Resaland G, et al. Optimal altitude for "living high-training low". Med Sci Sports Exerc 2002; 33 Suppl. 5: S292
65. Nummela A, Rusko H. Acclimatization to altitude and normoxic training improve 400-m running performance at sea level. J Sports Sci 2000 Jun; 18 (6): 411-9
66. Wilber RL, Shannon MP, Kearney JT, et al. Operational characteristics of a normobaric hypoxic system: proceedings of the Sixth International Olympic Committee World Congress on Sport Sciences. Med Sci Sports Exerc 2002; 34 Suppl. 5: 92
67. Shannon MP, Wilber RL, Kearney JT. Normobaric-hypoxia: performance characteristics of simulated altitude tents. Med Sci Sports Exerc 2001; 33 Suppl. 5: S60
68. Wilber RL. Live high-train low: thinking in terms of an optimal hypoxic dose. Int J Sports Physiol Performance 2007; 2: 223-38
69. Ge RL, Witkowski S, Zhang Y, et al. Determinants of erythropoietin release in response to short-term hypobaric hypoxia. J Appl Physiol 2002 Jun; 92 (6): 2361-7
70. Anchisi S, Moia C, Ferretti G. Oxygen delivery and oxygen return in humans exercising in acute normobaric hypoxia. Pflugers Arch 2001 Jun; 442 (3): 443-50
71. Woorons X, Mollard P, Pichon A, et al. Moderate exercise in hypoxia induces a greater arterial desaturation in trained than untrained men. Scand J Med Sci Sports 2007 Aug; 17 (4): 431-6
72. Townsend NE, Gore CJ, Hahn AG, et al. Living high-training low increases hypoxic ventilatory response of well-trained endurance athletes. J Appl Physiol 2002 Oct; 93 (4): 1498-505
73. Aughey RJ, Clark SA, Gore CJ, et al. Interspersed normoxia during live high, train low interventions reverses an early reduction in muscle Na+, K+ ATPase activity in well-trained athletes. Eur J Appl Physiol 2006 Oct; 98 (3): 299-309
74. Aughey RJ, Gore CJ, Hahn AG, et al. Chronic intermittent hypoxia and incremental cycling exercise independently depress muscle in vitro maximal Na+-K+-ATPase activity in well-trained athletes. J Appl Physiol 2005 Jan; 98 (1): 186-92
75. Girard O, Millet GP. Neuromuscular fatigue in racquet sports. Neurologic Clin 2008; 26 (1): 181-94
76. Powell FL, Garcia N. Physiological effects of intermittent hypoxia. High Alt Med Biol 2000 Summer; 1 (2): 125-36
77. Rodriguez FA, Casas H, Casas M, et al. Intermittent hypobaric hypoxia stimulates erythropoiesis and improves aerobic capacity. Med Sci Sports Exerc 1999 Feb; 31 (2): 264-8
78. Rodriguez FA, Ventura JL, Casas M, et al. Erythropoietin acute reaction and haematological adaptations to short, intermittent hypobaric hypoxia. Eur J Appl Physiol 2000 Jun; 82 (3): 170-7
79. Eckardt KU, Boutellier U, Kurtz A, et al. Rate of erythropoietin formation in humans in response to acute hypobaric hypoxia. J Appl Physiol 1989 Apr; 66 (4): 1785-8
80. Hellemans J. Intermittent hypoxic training: a pilot study. Proceedings of the Second Annual International Altitude Training Symposium; 1999 Feb 18-20; Flagstaff (AZ); 145-54
81. Knaupp W, Khilnani S, Sherwood J, et al. Erythropoietin response to acute normobaric hypoxia in humans. J Appl Physiol 1992 Sep; 73 (3): 837-40
82. Abellan R, Remacha AF, Ventura R, et al. Hematologic response to four weeks of intermittent hypobaric hypoxia in highly trained athletes. Haematologica 2005 Jan; 90 (1): 126-7
83. Ricart A, Casas H, Casas M, et al. Acclimatization near home? Early respiratory changes after short-term intermittent exposure to simulated altitude. Wilderness Environ Med 2000 Summer; 11 (2): 84-8
84. Frey WO, Zenhausern R, Colombani PC. Influence of intermittent exposure to normobaric hypoxia on hematological indexes and exercise performance [abstract]. Med Sci Sports 2000; 32 Suppl. 5: S65
85. Rodriguez FA, Murio J, Ventura JL. Effects of intermittent hypobaric hypoxia and altitude training on physiological and performance parameters in swimmers [abstract]. Med Sci Sports Exerc 2003; 35: S115
86. Julian CG, Gore CJ, Wilber RL, et al. Intermittent normobaric hypoxia does not alter performance or erythropoietic markers in highly trained distance runners. J Appl Physiol 2004 May; 96 (5): 1800-7
87. Tadibi V, Dehnert C, Menold E, et al. Unchanged anaerobic and aerobic performance after short-term intermittent hypoxia. Med Sci Sports Exerc 2007 May; 39 (5): 858-64

88. Woorons X, Mollard P, Lamberto C, et al. Effect of acute hypoxia on maximal exercise in trained and sedentary women. Med Sci Sports Exerc 2005 Jan; 37 (1): 147-54
89. Mollard P, Woorons X, Letournel M, et al. Role of maximal heart rate and arterial O2 saturation on the decrement of V̇O2max in moderate acute hypoxia in trained and untrained men. Int J Sports Med 2007 Mar; 28 (3): 186-92
90. Vogt M, Puntschart A, Geiser J, et al. Molecular adaptations in human skeletal muscle to endurance training under simulated hypoxic conditions. J Appl Physiol 2001 Jul; 91 (1): 173-82
91. Vallier JM, Chateau P, Guezennec CY. Effects of physical training in a hypobaric chamber on the physical performance of competitive triathletes. Eur J Appl Physiol Occup Physiol 1996; 73 (5): 471-8
92. Truijens MJ, Toussaint HM, Dow J, et al. Effect of high-intensity hypoxic training on sea-level swimming performances. J Appl Physiol 2003 Feb; 94 (2): 733-43
93. Emonson DL, Aminuddin AH, Wight RL, et al. Training-induced increases in sea level V̇O2max and endurance are not enhanced by acute hypobaric exposure. Eur J Appl Physiol Occup Physiol 1997; 76 (1): 8-12
94. Siri WE, Van Dyke DC, Winchell HS, et al. Early erythropoietin, blood, and physiological responses to severe hypoxia in man. J Appl Physiol 1966 Jan; 21 (1): 73-80
95. Levine BD, Stray-Gundersen J. A practical approach to altitude training: where to live and train for optimal performance enhancement. Int J Sports Med 1992 Oct; 13 Suppl 1: S209-12
96. Engfred K, Kjaer M, Secher NH, et al. Hypoxia and training-induced adaptation of hormonal responses to exercise in humans. Eur J Appl Physiol Occup Physiol 1994; 68 (4): 303-9
97. Terrados N, Melichna J, Sylven C, et al. Effects of training at simulated altitude on performance and muscle metabolic capacity in competitive road cyclists. Eur J Appl Physiol Occup Physiol 1988; 57 (2): 203-9
98. Schmidt W, Eckardt KU, Hilgendorf A, et al. Effects of maximal and submaximal exercise under normoxic and hypoxic conditions on serum erythropoietin level. Int J Sports Med 1991 Oct; 12 (5): 457-61
99. Casas M, Casas H, Pages T, et al. Intermittent hypobaric hypoxia induces altitude acclimation and improves the lactate threshold. Aviat Space Environ Med 2000 Feb; 71 (2): 125-30
100. Meeuwsen T, Hendriksen IJ, Holewijn M. Training-induced increases in sea-level performance are enhanced by acute intermittent hypobaric hypoxia. Eur J Appl Physiol 2001 Apr; 84 (4): 283-90
101. Melissa L, MacDougall JD, Tarnopolsky MA, et al. Skeletal muscle adaptations to training under normobaric hypoxic versus normoxic conditions. Med Sci Sports Exerc 1997 Feb; 29 (2): 238-43
102. Terrados N, Jansson E, Sylven C, et al. Is hypoxia a stimulus for synthesis of oxidative enzymes and myoglobin? J Appl Physiol 1990 Jun; 68 (6): 2369-72
103. Green H, MacDougall J, Tarnopolsky M, et al. Down-regulation of Na+-K+-ATPase pumps in skeletal muscle with training in normobaric hypoxia. J Appl Physiol 1999 May; 86 (5): 1745-8
104. Desplanches D, Hoppeler H, Linossier MT, et al. Effects of training in normoxia and normobaric hypoxia on human muscle ultrastructure. Pflugers Arch 1993 Nov; 425 (3-4): 263-7
105. Hoppeler H, Vogt M, Weibel ER, et al. Response of skeletal muscle mitochondria to hypoxia. Exp Physiol 2003 Jan; 88 (1): 109-19
106. Geiser J, Vogt M, Billeter R, et al. Training high-living low: changes of aerobic performance and muscle structure with training at simulated altitude. Int J Sports Med 2001 Nov; 22 (8): 579-85
107. Ponsot E, Dufour SP, Zoll J, et al. Exercise training in normobaric hypoxia in endurance runners. II: Improvement of mitochondrial properties in skeletal muscle. J Appl Physiol 2006 Apr; 100 (4): 1249-57
108. Coffey VG, Hawley JA. The molecular bases of training adaptation. Sports Med 2007; 37 (9): 737-63
109. Dufour SP, Ponsot E, Zoll J, et al. Exercise training in normobaric hypoxia in endurance runners. I: Improvement in aerobic performance capacity. J Appl Physiol 2006 Apr; 100 (4): 1238-48
110. Roels B, Bentley DJ, Coste O, et al. Effects of intermittent hypoxic training on cycling performance in well-trained athletes. Eur J Appl Physiol 2007 Oct; 101 (3): 359-68
111. Roels B, Thomas C, Bentley DJ, et al. Effects of intermittent hypoxic training on amino and fatty acid oxidative combustion in human permeabilized muscle fibers. J Appl Physiol 2007 Jan; 102 (1): 79-86
112. Morton JP, Cable NT. Effects of intermittent hypoxic training on aerobic and anaerobic performance. Ergonomics 2005 Sep 15-Nov 15; 48 (11-14): 1535-46
113. Woorons X, Mollard P, Pichon A, et al. Effects of a 4-week training with voluntary hypoventilation carried out at low pulmonary volumes. Respir Physiol Neurobiol 2008 Feb 1; 160 (2): 123-30
114. Woorons X, Mollard P, Pichon A, et al. Prolonged expiration down to residual volume leads to severe arterial hypoxemia in athletes during submaximal exercise. Respir Physiol Neurobiol 2007 Aug 15; 158 (1): 75-82
115. Hoppeler H, Vogt M. Muscle tissue adaptations to hypoxia. J Exp Biol 2001 Sep; 204 (Pt 18): 3133-9
116. Katayama K, Matsuo H, Ishida K, et al. Intermittent hypoxia improves endurance performance and submaximal exercise efficiency. High Alt Med Biol 2003 Fall; 4 (3): 291-304
117. Wilber RL, Stray-Gundersen J, Levine BD. Effect of hypoxic "dose" on physiological responses and sea-level performance. Med Sci Sports Exerc 2007 Sep; 39 (9): 1590-9
118. Sevre K, Bendz B, Hanko E, et al. Reduced autonomic activity during stepwise exposure to high altitude. Acta Physiol Scand 2001 Dec; 173 (4): 409-17
119. Fiskerstrand A, Seiler KS. Training and performance characteristics among Norwegian international rowers 1970-2001. Scand J Med Sci Sports 2004 Oct; 14 (5): 303-10
120. Seiler KS, Kjerland GO. Quantifying training intensity distribution in elite endurance athletes: is there evidence for an "optimal" distribution? Scand J Med Sci Sports 2006 Feb; 16 (1): 49-56
121. Seiler S, Haugen O, Kuffel E. Autonomic recovery after exercise in trained athletes: intensity and duration effects. Med Sci Sports Exerc 2007 Aug; 39 (8): 1366-73

122. Esteve-Lanao J, Foster C, Seiler S, et al. Impact of training intensity distribution on performance in endurance athletes. J Strength Cond Res 2007 Aug; 21 (3): 943-9
123. Esteve-Lanao J, San Juan AF, Earnest CP, et al. How do endurance runners actually train? Relationship with competition performance. Med Sci Sports Exerc 2005 Mar; 37 (3): 496-504
124. Yamamoto K, Miyachi M, Saitoh T, et al. Effects of endurance training on resting and post-exercise cardiac autonomic control. Med Sci Sports Exerc 2001 Sep; 33 (9): 1496-502
125. Bernardi L, Passino C, Serebrovskaya Z, et al. Respiratory and cardiovascular adaptations to progressive hypoxia: effect of interval hypoxic training. Eur Heart J 2001 May; 22 (10): 879-86

Correspondence: Dr *Gregoire P. Millet*, ISSUL, Institute of Sport Science, University of Lausanne, CH-1015, Lausanne, Switzerland.
E-mail: gregoire.millet@unil.ch