Intermittent Hypoxic Training: Fact and Fancy

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ABSTRACT

Levine, Benjamin D., Intermittent hypoxic training: Fact and fancy. *High Alt Med Biol.* 3:177–193, 2002.—Intermittent hypoxic training (IHT) refers to the discontinuous use of normobaric or hypobaric hypoxia, in an attempt to reproduce some of the key features of altitude acclimatization, with the ultimate goal to improve sea-level athletic performance. In general, IHT can be divided into two different strategies: (1) providing hypoxia *at rest* with the primary goal being to stimulate altitude acclimatization or (2) providing hypoxia *during exercise*, with the primary goal being to enhance the training stimulus. Each approach has many different possible application strategies, with the essential variable among them being the "dose" of hypoxia necessary to achieve the desired effect. One approach, called living high–training low, has been shown to improve sea-level endurance performance. This strategy combines altitude acclimatization (2500 m) with low altitude training to ensure high-quality training. The opposite strategy, living low–training high, has also been proposed by some investigators. The primacy of the altitude acclimatization effect in IHT is demonstrated by the following facts: (1) living high–training low clearly improves performance in athletes of all abilities, (2) the mechanism of this improvement is primarily an increase in erythropoietin, leading to increased red cell mass, $V_{O_{2}max}$, and running performance, and (3) rather than intensifying the training stimulus, training at altitude or under hypoxia leads to the opposite effect—reduced speeds, reduced power output, reduced oxygen flux—and therefore is not likely to provide any advantage for a well-trained athlete.

Key Words: hypoxia; hypobaria; altitude; exercise; athletes

ALTITUDE TRAINING has been used frequently by endurance athletes to enhance performance. However, not all athletes or teams have the resources to travel to high altitude environments on a regular basis. Moreover, issues such as availability of adequate training facilities have limited the use of mountain-based altitude training. In the last few years, there has been a remarkable increase in the number of techniques designed to "bring the mountain to the athlete." Nitrogen houses, hypoxia tents, and special breathing apparatuses to provide inspired hypoxia at rest and during exercise, all have been developed and promoted to simulate what are perceived as the critical elements of altitude training.

Intermittent hypoxic training (IHT) refers to the discontinuous use of normobaric or hypobaric hypoxia, in an attempt to reproduce some of these key features of altitude acclimatization, with the ultimate goal to improve sea-level athletic performance. In general, IHT can be divided into two different strategies: (1) providing hypoxia *at rest* with

the primary goal being to stimulate altitude acclimatization or (2) providing hypoxia *during exercise*, with the primary goal being to enhance the training stimulus. Each approach has many different possible application strategies, with the essential variable among them being the "dose" of hypoxia necessary to achieve the desired effect—how severe is the hypoxic stimulus, how long should each exposure be (how many minutes or hours per day), how often should the stimulus be delivered (how many days per week), and for what duration should the stimulus persist (how many weeks or months per year)? Unfortunately, there are very few studies comparing one strategy against the other in an objective fashion.

HYPOXIA AT REST

Continuous exposure to hypobaric hypoxia at rest, either as real or simulated high altitude, stimulates the process of acclimatization, which includes a number of physiological adaptations that improve the ability to perform work at altitude and might be advantageous for exercise performance at sea level. The majority of these clearly improve *submaximal* work performance while at altitude (Maher et al., 1974), though they do not return maximal exercise performance to prealtitude levels (Saltin et al., 1968). For example, increases in alveolar ventilation and reductions in mixed venous oxygen content are primarily responsible for maximizing exercise capacity at high altitudes (Sutton et al., 1988). Substrate utilization is altered after acclimatization, with some evidence for changes in both fat (Roberts et al., 1996) and carbohydrate (Brooks et al., 1991a,b, 1992) metabolism. This results in decreased metabolite accumulation such as lactate (Young et al., 1982; Brooks et al., 1991a; Wolfel et al., 1991) or ammonia (Young et al., 1987) during submaximal exercise and, in some cases, sparing of muscle glycogen (Young et al., 1982). However, results regarding metabolic changes vary widely among investigations depending on the absolute altitude achieved, training state prior to study, and whether absolute or relative workloads were compared (Wolfel et al., 1991;

Brooks et al., 1992; Mazzeo et al., 1994; Roberts et al., 1996; McClelland et al., 1998; Brooks 1999). Some animal studies have suggested that peripheral uptake of oxygen by skeletal muscle may be facilitated by increased capillary density (Tenney and Ou, 1970; Banchero, 1975), mitochondrial number (Ou et al., 1970), and tissue myoglobin concentration (Reynafarje et al., 1975), as well as by increased concentrations of 2,3-DPG (Mairbaurl et al., 1986; Mairbaurl, 1989; Mairbaurl and Schobersberger, 1990). However, these adaptations have been much more difficult to demonstrate in humans (Green et al., 1989). In fact, reductions in muscle fiber size, rather than a true increase in capillary number, may be the most prominent manifestation of sustained exposure to moderate or high altitude (Green et al., 1989; MacDougall et al., 1991). Recently, alterations in the sodium–potassium pump have been described after climbing expeditions (Green et al., 1999), though whether hypoxia or some other stimulus (alterations in training state, nutritional changes, cold, stress, etc.) is responsible for this adaptation is not clear. Finally, some studies have reported that buffer capacity of skeletal muscle may be increased (Mizuno et al., 1990), even with discontinuous altitude exposure (Gore et al., 2001), which may improve anaerobic capacity and endurance. Together, these adaptations may be sufficient to restore exercise capacity to near sea-level values at low or moderate altitudes of <2500 m. At higher altitudes, acclimatization is not sufficient to restore $V_{O_{2max}}$ to normal (Saltin et al., 1968), and even acute erythrocyte infusion is not beneficial (Young et al., 1996). The importance of most of these adaptations for sea-level performance, however, remains unproved.

ERYTHROPOIETIC EFFECT OF HIGH ALTITUDE

In contrast, the adaptation that has been observed with continuous altitude exposure that has the clearest link to improved sea-level performance is an increase in hemoglobin and hematocrit, which increases the oxygen-carrying capacity of the blood and improves aerobic power (Ekblom et al., 1972; Buick et al., 1980;

Williams et al., 1981; Ekblom and Berglund, 1991; Birkeland et al., 2000). Although some studies in elite athletes have failed to show an increase in red blood cell mass with chronic altitude exposure (Gore et al., 1998), the sum of experimental evidence in favor of this response is quite compelling. First, cross-sectional studies in the Peruvian Andes (Hurtado et al., 1945; Reynafarje et al., 1959; Sanchez et al., 1970), as well as in the Colorado Rockies (Weil et al., 1968), have demonstrated clearly that there is an elevated red cell mass in natives of high altitude. These studies were done using many different techniques for estimating the red cell mass, including radioactive chromium, iron, and phosphorus compounds, as well as Evans Blue and Vital Red dyes, and all show the same result: an increase in red cell mass with chronic hypobaric hypoxia. Moreover, by looking at populations living at different altitudes, a graded response has been identified, with an increase in red cell mass that is proportional to the oxyhemoglobin saturation (Hurtado et al., 1945; Weil et al., 1968).

As expected from the cross-sectional studies, when sea-level natives ascend acutely to altitude, there is an increase in iron turnover by more than twofold that begins within the first few hours of exposure and peaks by approximately 2 to 3 weeks (Huff et al., 1951; Reynafarje et al., 1959; Faura et al., 1969). Direct examination of the bone marrow during acute high altitude exposure has documented a dramatic increase in nucleated red blood cells, virtually doubling by 7 d, indicative of accelerated erythropoiesis (Huff et al., 1951; Reynafarje et al., 1959). Thus the evidence is very strong that a key component of the altitude-mediated effect of "altitude training" is the erythropoietic effect of chronic exposure to hypoxia. But how long does an athlete have to live at altitude or remain in a simulated hypoxic environment to attain this effect?

Several investigations indicate that short bursts (84 to 114 min depending on the severity of hypoxia) of hypobaric hypoxia provide a stimulus sufficient to elicit an increase in erythropoietin (Abbrecht et al., 1972; Eckardt et al., 1989). Although increases in hematocrit and hemoglobin concentration have been reported with repeated short-term exposures (Rodri-

guez et al., 1999), whether accelerated erythropoiesis actually occurs, leading to a true increase in red cell mass and/or blood volume, is not clear (Garcia et al., 2000). For example, Garcia et al. (2 h/d for 5 d at simulated altitude of 3800 m) (Garcia et al., 2000) and Piel-Aulin et al. (12 h/d at 2000 or 2700 m for 10 d) (Piehl Aulin et al., 1998) have reported that intermittent hypobaric hypoxic exposure significantly increases blood reticulocyte count. Follow-up investigations suggested that exposure to 5000 m, 3 h/d for 9 days was sufficient to significantly increase RBC count, reticulocyte number, and hemoglobin concentration (Rodriguez et al., 1999). In longer-term studies by the same group of investigators, erythropoietin concentrations increased significantly, by approximately 50% with an acute 90-min acute exposure to 3500 m (Rodriguez et al., 2000). When exposure to simulated altitudes up to 5000 m was administered three times at 90 min/week for 3 weeks (modeling clinical studies using EPO to treat anemia in patients on dialysis), red blood cell count, reticulocytes, and hemoglobin concentration increased, with peak values observed at the end of the protocol and/or during the subsequent 2 weeks. However, clinical experience with direct injection of recombinant erythropoietin, which yields much higher acute concentrations of erythropoietin, would argue that such short exposures would be very unlikely to actually increase the red cell mass (Ashenden et al., 2001); usually a minimum of 2 weeks of regular injections of EPO is required before a measurable erythropoietic effect is identified. Moreover, it is important to recognize that short-term exposure to acute hypoxia may increase hematocrit and hemoglobin concentration by hemoconcentration and may increase reticulocyte counts by release of immature red cell forms from the bone marrow, without a true acceleration of erythropoiesis (Gunga et al., 1996).

Some investigators, failing to observe an increase in hemoglobin–myoglobin mass after brief periods of time in normobaric hypoxic environments (8 to 10 h/night for 10 d for 3 weeks) have questioned the erythropoietic effect of moderate altitude exposure altogether (Ashenden et al., 1999a, 1999b, 2000), and it seems certain from these data that, under the

specific conditions of these experiments, sleeping in a nitrogen-enriched environment may in fact not be erythropoietic. Although short-duration exposures of less than 10 h for less than 3 weeks do not raise red cell mass in the Australian experience (Ashenden et al., 1999a, 1999b, 2000), Finnish investigators have been able to demonstrate increases in red cell mass (using the same technique, carbon monoxide rebreathing, as the Australian investigators using shorter-term exposures) with 16 h of hypoxia/night for 4 weeks (Laitinen et al., 1995; Rusko et al., 1999). Together, these data suggest that there is a definite threshold effect, but how this minimal "dose" is related to the absolute magnitude of hypoxia achieved, duration of exposure per day, or total exposure over time is uncertain.

Recent advances in understanding of the biological pathways involved in the adaptive response to hypoxia have the potential to contribute substantially to this debate. For example, the principal transcriptional activator of gene expression in hypoxic cells is hypoxia-inducible factor 1 (HIF-1) (Semenza, 1994; Semenza et al., 1994; Wang and Semenza, 1996; Semenza et al., 1997). Under normal, well-oxygenated conditions, HIF-1 is hydroxylated via a highly conserved prolyl hydroxylase (the putative cellular "oxygen sensor" in peripheral tissues), which then binds to the Von Hipple–Lindau factor, targeting the entire complex for rapid degradation via the ubiquitin–proteosome pathway (Epstein et al., 2001; Ivan et al., 2001; Jaakkola et al., 2001). In fact, this process is so rapid that, in the presence of oxygen and iron, HIF-1α has one of the shortest half-lives of any known protein (Wang et al., 1995; Jaakkola et al., 2001). In contrast, under hypoxic conditions, the HIF-1 complex is stable, allowing for transcriptional activation and ultimate stimulation of proteins such as erythropoietin and vascular endothelial growth factor (Wang and Semenza, 1996).

Interestingly, both erythropoietin concentrations (Jelkman, 1992; Richalet et al., 1993; Gunga et al., 1996; Levine and Stray-Gundersen, 1997; Chapman et al., 1998), as well as iron turnover (Huff et al., 1951; Reynafarje et al., 1959) return to sea-level values relatively rapidly with chronic altitude exposure. How-
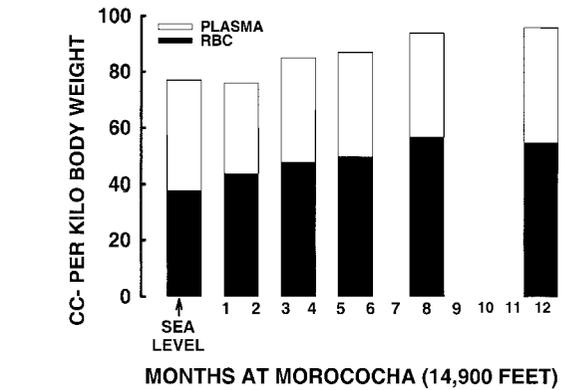

FIG. 1. Change in plasma and red cell volume in sea-level natives transported to high altitude over a continuous 1-yr period. Note continuous rise in red cell volume through 8 months of high altitude residence. From Reynafarje et al., 1959.

ever, the red cell mass continues to increase for up to 8 months of chronic altitude exposure, at least at altitudes above 4000 m (Reynafarje et al., 1959) (Fig. 1). Moreover, despite the apparently normal EPO levels and iron turnover, it is important to point out that this level of stimulated erythropoiesis is elevated for the absolute level of the arterial oxygen content. Thus, when altitude natives, or even altitude sojourners, return to sea level, there is a suppression of erythropoietin (Faura et al., 1969; Jelkman, 1992; Richalet et al., 1993; Gunga et al., 1996; Levine and Stray-Gundersen, 1997; Chapman et al., 1998), a dramatic reduction in iron turnover and bone marrow production of erythroid cell lines (Huff et al., 1951; Reynafarje et al., 1959), and a marked decrease in red cell survival time (Reynafarje et al., 1959). This increase in red cell destruction with suppression of EPO levels has been termed *neocytolysis* and has been observed under other conditions of a relative increase in oxygen content (Alfrey et al., 1996a, 1996b, 1997; Rice and Alfrey, 2000; Rice et al., 2001). Both the rapid ubiquitination and destruction of HIF-1α and neocytolysis (which may be its clinical manifestation) may compromise the ability of short-duration, intermittent hypoxic exposures to induce a sustained increase in the red cell mass.

Finally, erythropoietin itself must then circulate to the bone marrow, where it binds to the EPO receptor, which ultimately leads to the acceleration of erythropoieis (Prchal and Pr-

chal, 1999). Genetic variability clearly plays an important role in both animal (Ou et al., 1998) and human studies (Juvonen et al., 1991) in determining at least some of the variability in the response to hypoxia, and it seems simplistic to expect a simple linear relationship among any of these variables to be easily identified in humans. For example, one recent human study showed that in a large group of healthy young athletes the increase in EPO measured after 24 h at 3000 m simulated altitude ranged from +400% to −40% (Ri-Li et al., 2002). Preliminary evidence suggests that at least some of this variability may be related to a genetic polymorphism associated with the EPO gene (Witkowski et al., 2002). More work must be done to define the dose–response relationship under these circumstances and to determine the genetic mechanisms responsible for individual variability.

THE LIVING HIGH–TRAINING LOW MODEL

Much of the modern interest in intermittent hypoxic training derives from the elaboration of the living high–training low model by Levine and Stray-Gundersen, which has been shown to improve sea-level performance in endurance sports (Levine et al., 1992; Levine and Stray-Gundersen, 1997). This strategy combines moderate altitude acclimatization (2500 m) with low altitude training to get the optimal effect. Although it is a form of "intermittent hypoxia" in the strictest sense of the term, it would probably be most accurate to call this approach "intermittent normoxia" since the athletes in these studies spent more than 20 h/day in a hypobaric hypoxic environment.

The living high–training low model was confirmed in a series of carefully controlled studies (Levine et al., 1992; Levine and Stray-Gundersen, 1997; Stray-Gundersen and Levine, 1997; Chapman et al., 1998), which have a number of important features that deserve emphasis: (1) all studies began with a 2-week lead-in phase in which athletes were brought from their home cities to Dallas, Texas (150 m above sea level) for familiarization with laboratory equipment and testing procedures, and a fo-

cused period of controlled training to overcome the training camp effect. This strategy derived from pilot work that showed that training camps generally resulted in an increase in $V_{O_{2max}}$ and improved performance in collegiate runners regardless of where they lived and trained. Subsequently, in one pilot study designed to determine the minimum duration of training required to observe this effect, six male runners increased their $V_{O_{2max}}$ from 68 ± 1.5 to 70 ± 1.4 mL/kg/min after 2 weeks of supervised training at sea level, but did not increase further after an additional 2 weeks of training (70 ± 1.8 mL/kg/min) (Levine and Stray-Gundersen, unpublished observations); (2) this lead-in phase was followed by a 4-week mesocycle of training at sea level, where all athletes trained together prior to randomization to bring all athletes up to an equivalent degree of training readiness and to provide a longitudinal control for the experimental intervention. This period also allowed additional time to restore bone marrow iron stores in those athletes who were iron deficient. Previous work by the authors (Stray-Gundersen et al., 1993, 1995) and others (Hannon et al., 1969) demonstrated that individuals who are iron deficient are unable to increase the red cell mass in response to altitude exposure; (3) athletes were then randomized into one of three training groups ($n = 13$ for each; 9 men, 4 women), where they were exposed for 4 weeks to (a) the primary experimental group, where the athletes lived at 2500 m and traveled down to a lower altitude of 1250 m once or twice per day to train (high–low); (b) an altitude control (high–high), where the athletes lived at 2500 m together with the hi-lo athletes, but did all their training at the same altitude or higher (2500–3000 m); and (c) a sea-level control, where the athletes traveled to a new training camp environment with mountainous terrain, but at sea-level altitude (low–low). The volume and relative intensity of training were closely matched among groups and followed the same pattern as the previous 4 weeks of training at sea level. All subjects then returned to sea level for postintervention testing.

The essential results of these studies were as follows: (1) The groups living at 2500 m had a significant increase in erythropoietin concen-

tration within the first 48 h of ascent to altitude, which led to a significant increase in the erythrocyte volume (blood volume–plasma volume); neither changed significantly in the sea-level control. (2) Coincident with the increase in erythrocyte volume, there was an increase in maximal oxygen uptake in both groups living at 2500 m (Fig. 2) that was proportional to the increase in erythrocyte volume and that was not observed in the control group performing similar training in an outstanding training camp environment, but at sea level. (3) Despite an increase in $V_{O_{2max}}$ in both groups of subjects living at moderate altitude, only the group performing all their training at low altitude improved 5000 m racing time by 1.3% (Fig. 3).

If both groups of athletes living at 2500 m increased erythrocyte volume and $V_{O_{2max}}$, then why didn't both groups improve running performance? Based on previous reports that muscle buffer capacity might increase with altitude exposure (Mizuno et al., 1990), one possibility that was considered was that "anaerobic" performance was improved more by living high–training low. Another possibility raised by some investigators was that exercise economy (cycling) might be altered by altitude ac-
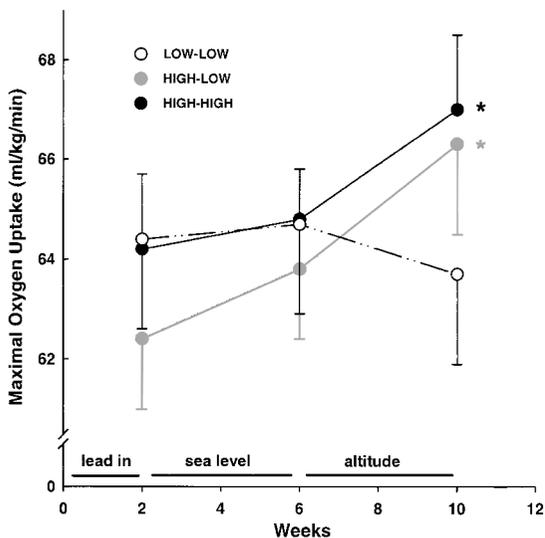

FIG. 3. Note improvement in 5K time in all groups after initial training at sea level, which only improved further in the high–low group. Data shown are for men only because of marked variability in response of some of the control women. From Levine and Stray-Gundersen, 1997.

climatization (Green et al., 1999; Gore et al., 2001), though data to support this hypothesis are limited. However, in the studies by Levine and Stray-Gundersen, neither the accumulated oxygen deficit (measured by uphill running on a treadmill (Medbo et al., 1988) (Fig. 4) nor the running economy (measured as the slope of the relationship between running speed at 8, 10, and 12 miles/h and oxygen uptake) was different among groups or altered by training either at altitude or at sea level (Levine and Stray-Gundersen, 1997).

The key difference between the high–high and the high–low altitude groups was that the high–low group performed all their training at low altitude and thus were able to maintain both training velocity and oxygen flux during high-intensity "interval"-type training sessions that are essential for the performance of competitive runners. These sessions (1000-m intervals run at 110% of race pace) were run at slower speeds, reduced oxygen uptake, lower heart rate, and lower peak lactate in the athletes performing all their training at 2500 m than the same sessions run either at 1250 m or at sea level (Levine and Stray-Gundersen, 1997), as has been noted by the authors in other groups of athletes (Levine and Stray-Gundersen, 1992), as well as by other investigators (Brosnan et al., 2000). For the high–low athletes,

FIG. 2. Change in maximal oxygen uptake after sea-level lead-in phase, followed by living at 2500 m and training at 2500 to 3000 m (high–high), living at 2500 m and training at 1250 m (high–low), or living and training at sea level (low–low). From Levine and Stray-Gundersen, 1997.
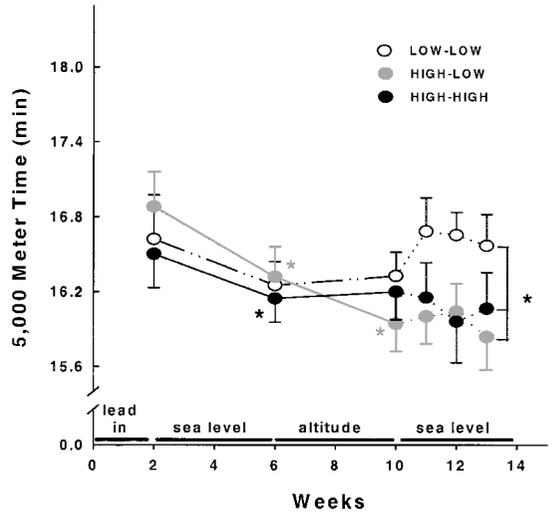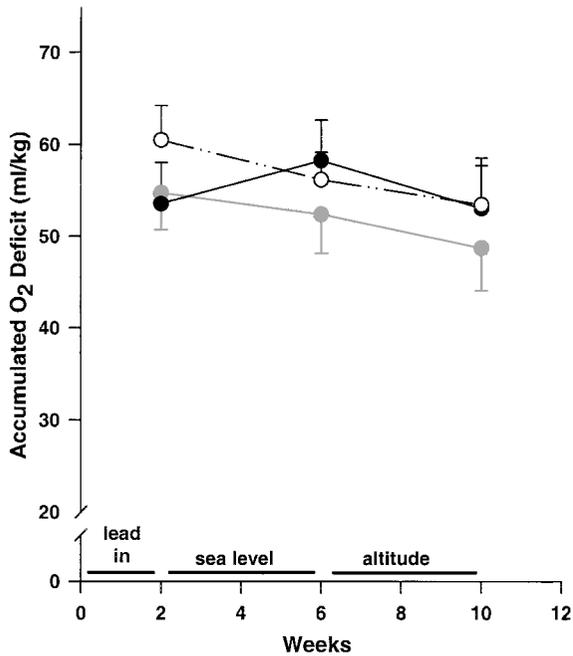
FIG. 4. Data derived from Levine and Stray-Gundersen, 1997, originally presented only in table form. Symbols are the same as in Figs. 1 and 2, with open symbols representing living low–training low, filled symbols representing living high–training high, and gray symbols representing living high–training low.

this quality of training maintained muscle fiber size, myoglobin concentration, and muscle buffer capacity, all of which decreased in the athletes attempting to do all their training at moderate altitude (Stray-Gundersen and Levine, 1999). Functionally, this preservation of muscle structure allowed an increase in both the V_{O_2} at the ventilatory threshold and the velocity at $V_{O_{2max}}$, which were present only in the high–low group (Levine and Stray-Gundersen, 1997).

The essential nature of maintaining speed and oxygen flux primarily during interval training was confirmed in a subsequent follow-up study (Stray-Gundersen and Levine, 1997), in which another group of 13 athletes lived at 2500 m, performed all their base and recovery training at moderate altitude (2000 to 3000 m), but performed all their high-intensity training at low altitude (1250 m) (high–high–low). These athletes had virtually identical improvements in performance compared with the high–low athletes who did all their training at low altitude (Fig. 5).

Not only does this living high–training low

strategy work for good collegiate athletes, but recent data suggest that it also works for elite athletes. Stray-Gundersen et al. examined 27 elite male and female U.S. distance runners immediately after their national championship competition when they were at their peak performance for the year. After baseline measurements, all performed 4 weeks of living at 2500 m, easy training at 2000 to 3000 m, and high-intensity training at 1250 m (Stray-Gundersen et al., 2001). Even for athletes who began with $V_{O_{2max}}$ levels above 80 mL/kg/min, the improvement in $V_{O_{2max}}$ and racing performance was similar to that observed in the collegiate athletes and equivalent between men and women (Stray-Gundersen et al., 2001).

Despite the clear superiority of living high–training low over traditional altitude or sea-level training, there remains substantial individual variability in the magnitude of improvement achieved with such a regimen. At least some of this variability in previous studies and in the practice of athletes is likely due to iron deficiency. In our experience, approximately 40% of competitive distance runners (20% male, 60% female runners) have a serum ferritin that is suggestive of reduced bone marrow iron stores (Stray-Gundersen et al., 1993, 1995). When such athletes attempt altitude training, they often do not thrive and clearly do not increase erythrocyte volume or $V_{O_{2max}}$ (Levine and Stray-Gundersen, 1996). However, even in studies in which iron stores were replenished, there remains substantial variability in the outcome of a 4-week altitude training camp. To address the mechanisms of this variability, Chapman et al. (Chapman et al., 1998) performed a retrospective review of all 39 athletes in the Levine and Stray-Gundersen studies (Levine and Stray-Gundersen, 1997; Stray-Gundersen and Levine, 1997), who lived at 2500 m and trained between 1250 m and 3000 m, and divided them into two groups: those athletes who improved their 5000 race by more than the group mean (responders) and those that got worse (nonresponders) (Fig. 6). There were no differences between these groups with respect to baseline demographic variables (age, $V_{O_{2max}}$, running performance, hemoglobin concentration) or many physiological variables that might determine the magnitude of the ac-
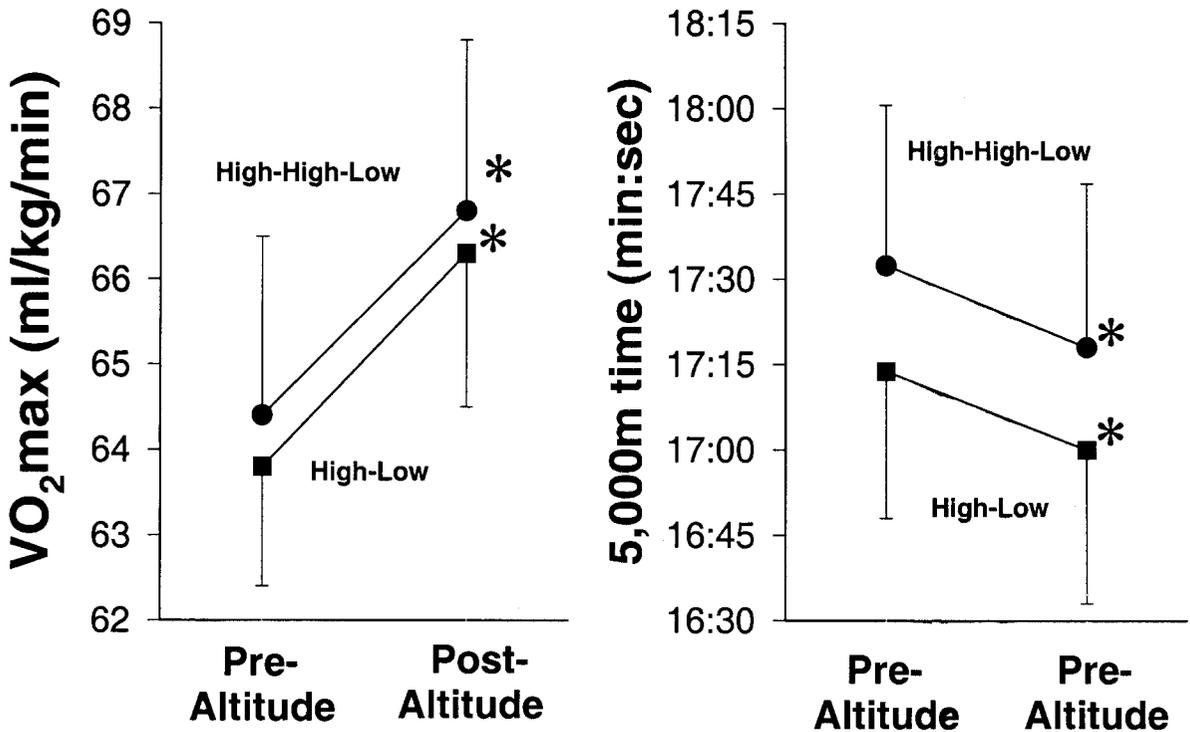
FIG. 5. High–low data from Levine and Stray-Gundersen, 1997; high–high–low data from Stray-Gundersen and Levine, 1997. Prealtitude data were obtained after completion of lead-in and sea-level training phases; $n = 13$, 9 men, 4 women, for both groups using identical methods.

climatization response to altitude, including pulmonary diffusing capacity and oxygen saturation either at rest, during sleep, or during exercise at 2500 m.

However, there were a number of key distinguishing features between these two groups. First, although both groups increased erythropoietin concentration after 24 h at 2500 m, the responders had a significantly greater increase; moreover, the erythropoietin concentration remained elevated after 2 weeks at moderate altitude in the responders (equivalent to the peak response in the nonresponders), while it had returned to baseline in the nonresponders (Fig. 7).

Not only was the increase in erythropoietin more robust in the responders, but this difference also appeared to carry substantial physiological significance. Specifically, the responders had an increase in erythrocyte volume, while the nonresponders did not. Moreover, this increase in red cells increased aerobic power: the responders had an increase in V_{O_2max}, while the nonresponders did not. Finally, the increase in V_{O_2max} was exactly what would be predicted from published models

quantifying the effect of a change in blood volume and hemoglobin concentration on aerobic power (Warren and Cureton, 1989): predicted increase was 248 mL/min; actual increase was 245 mL/min (Chapman et al., 1998). Thus the magnitude of the altitude effect is exactly what would be expected from the well-known effect of blood doping (Buick et al., 1980; Williams et al., 1981; Ekblom and Berglund, 1991) or exogenous erythropoietin injection (Ekblom and Berglund, 1991; Birkeland et al., 2000).

In addition to this different erythropoietic response, the responders, regardless of the altitude at which they trained, had a smaller decrease in running speed and oxygen uptake during interval training sessions compared to the nonresponders. In other words, the responders were better able to maintain normal training velocities and oxygen flux at altitude than the nonresponders. These two parallel pathways, the erythropoietic mechanism and the training quality pathway, are pictured in Fig. 8, from Chapman et al. (1998). Finally, this retrospectively derived formula of distinguishing between responders and nonresponders by
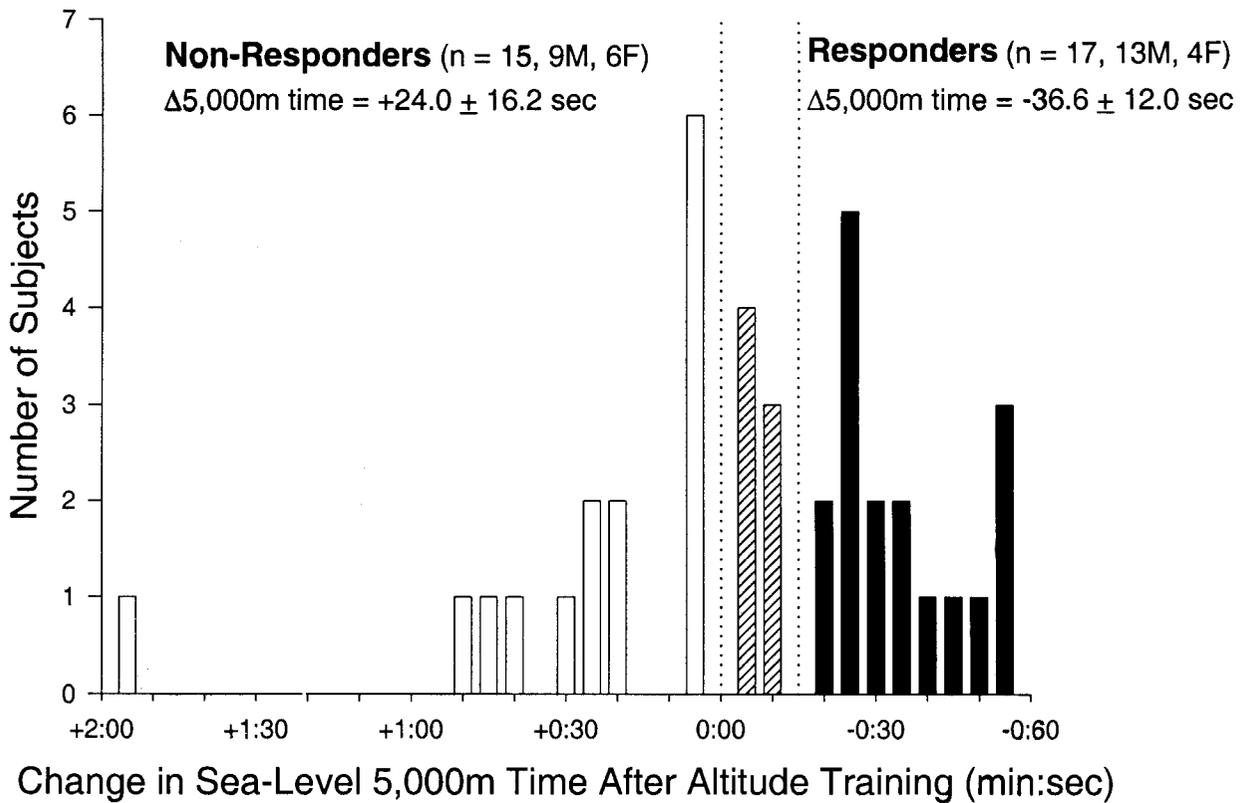
FIG. 6. Histogram showing the change in 5000-m run time after 4 weeks of living at 2500 m and training at either 2500 to 3000 m, all training at 1250 m, or only interval training at 1250 m. Hatched bars represent athletes with an intermediate response and were not included in the analysis. From Chapman et al., 1998.

examining the erythropoeitic response to altitude was applied prospectively to an entirely different population of elite athletes, with essentially the same result: both erythropoietin concentration and $V_{O_{2max}}$ increased significantly in those responders who improved by more than the mean response for the group, while neither increased significantly in those who got slower.

In summary, these studies demonstrate convincingly that (1) the living high–training low model of intermittent hypoxic training works to improve sea-level performance, (2) the mechanism is highly likely to be a stimulation of erythropoiesis, leading to an increase in hemoglobin concentration, total blood volume, and aerobic power, and (3) the effect of this increase in oxygen transport capacity is maximized by maintaining normal, sea-level oxygen flux during intense exercise, thus avoiding the downregulation of skeletal muscle structure and function that may occur in athletes who at-

tempt to perform all their training under hypoxic conditions.

HYPOXIA DURING EXERCISE

Despite the compelling nature of these studies, there remains a question among some investigators whether hypoxic exercise, under the right conditions, could enhance the training stimulus. Certainly, performing exercise in hypoxia "feels harder," with increased ventilation, heart rate, and lactate during submaximal exercise (Mazzeo et al., 1991; Wolfel, 1993). Moreover, Vogt et al. (2001) recently have demonstrated augmented transcription of mRNA for HIF-1α in subjects training in hypoxia (equivalent to an altitude of 3850 m) compared to normoxia, as well as increased mRNA for myoglobin and vascular endothelial growth factor if the exercise performed was of high intensity. However, they were unable to demon-
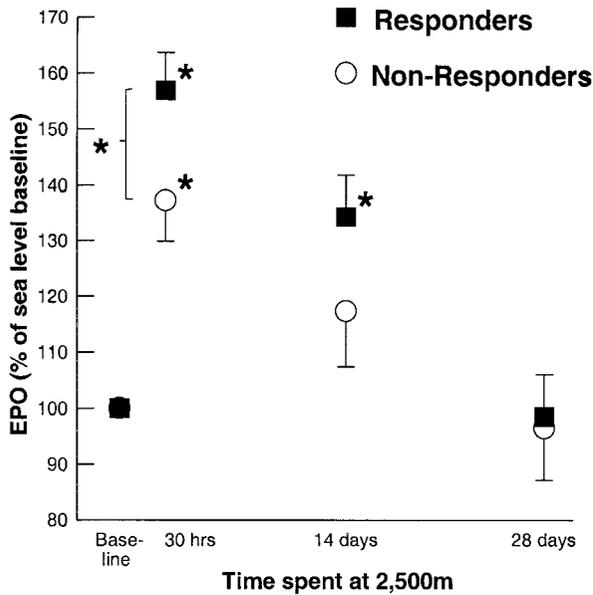
FIG. 7. Change in erythropoietin concentration after 24 h at 2500 m in responders and nonresponders. Note that the EPO level in the responders after 2 weeks is equivalent to the peak response of the nonresponders acutely, who by 2 weeks have returned to baseline. From Chapman et al., 1998.

strate a functional outcome of this change at the molecular level; both $V_{O_{2max}}$ and maximal power output were increased equally in both groups. It is possible that the extremely rapid ubiquitination and subsequent destruction of the VHL–HIF-1α complex under normoxic conditions (Wang et al., 1995) may explain the failure of such short-term hypoxia to lead to physiologically significant translational effects.

Probably the most persuasive data arguing for a beneficial effect of hypoxic exercise were presented by Terrados and colleagues (1990). These investigators performed a beautifully designed experiment in which one leg was trained under hypobaric hypoxic conditions and the other leg served as the control, exercising at exactly the same absolute work rate. They demonstrated in these relatively untrained subjects a greater increase in endurance, and a greater increase in both citrate synthase activity and myoglobin concentration in the leg that trained in hypoxia.

However, this study used a relatively small muscle mass (one leg) in which muscle blood flow and oxygen delivery were not limited to exercise performance. Multiple investigations using whole-body, systemic exercise in hypoxia

have been less convincing. For example, Roskamm et al. (1969) studied 18 untrained male students randomly assigned to train for 4 weeks in a hypobaric chamber, at either sea level, 2250 m, or 3450 m. Each subject trained for 30/min/day, 6 d/week in the altitude chamber for 4 weeks. There was a large variation in the increase in $V_{O_{2max}}$, ranging from 6.4% to 17.5%, with no statistically different differences among groups. Of note, no increase in hemoglobin was observed in any of the three groups.

A well-controlled study was performed by Loeppky and Bynum (1970) in which nine fit subjects exercised in a hypobaric chamber, at either a control altitude of 628 torr (1575 m) or 523 torr (3050 m), with the subjects blinded as to the altitude. Subjects exercised for 1 h/day; treadmill running, cycle ergometry, and calisthenics were done at progressively increasing altitudes from 3050 to 4270 m. There was no significant difference for the increase in $V_{O_{2max}}$ in the altitude-trained group ($n = 5$) compared to the control group ($n = 4$); however, total running time on the incremental test used to measure $V_{O_{2max}}$ did improve to a significantly greater extent in the altitude-trained group compared to control, suggesting the possibility of an increase in oxygen debt and possibly anaerobic capacity. Like Roskamm and colleagues, these authors reported no changes in hemoglobin or hematocrit.

A number of other studies have investigated the effects of intermittent hypoxic training in relatively untrained subjects (Levine and Stray-Gundersen, 1992; Emonson et al., 1997) with the same result. Together these studies showed clearly that intermittent hypoxic training has no beneficial effect over equivalent training at sea level in untrained subjects during whole-body exercise. In such individuals, the effect of training seems to predominate, overwhelming any additional effect of hypoxia. However, this result might be different in already well-trained athletes in whom the effect of training per se has been maximized.

HYPOXIC EXERCISE IN COMPETITIVE ATHLETES

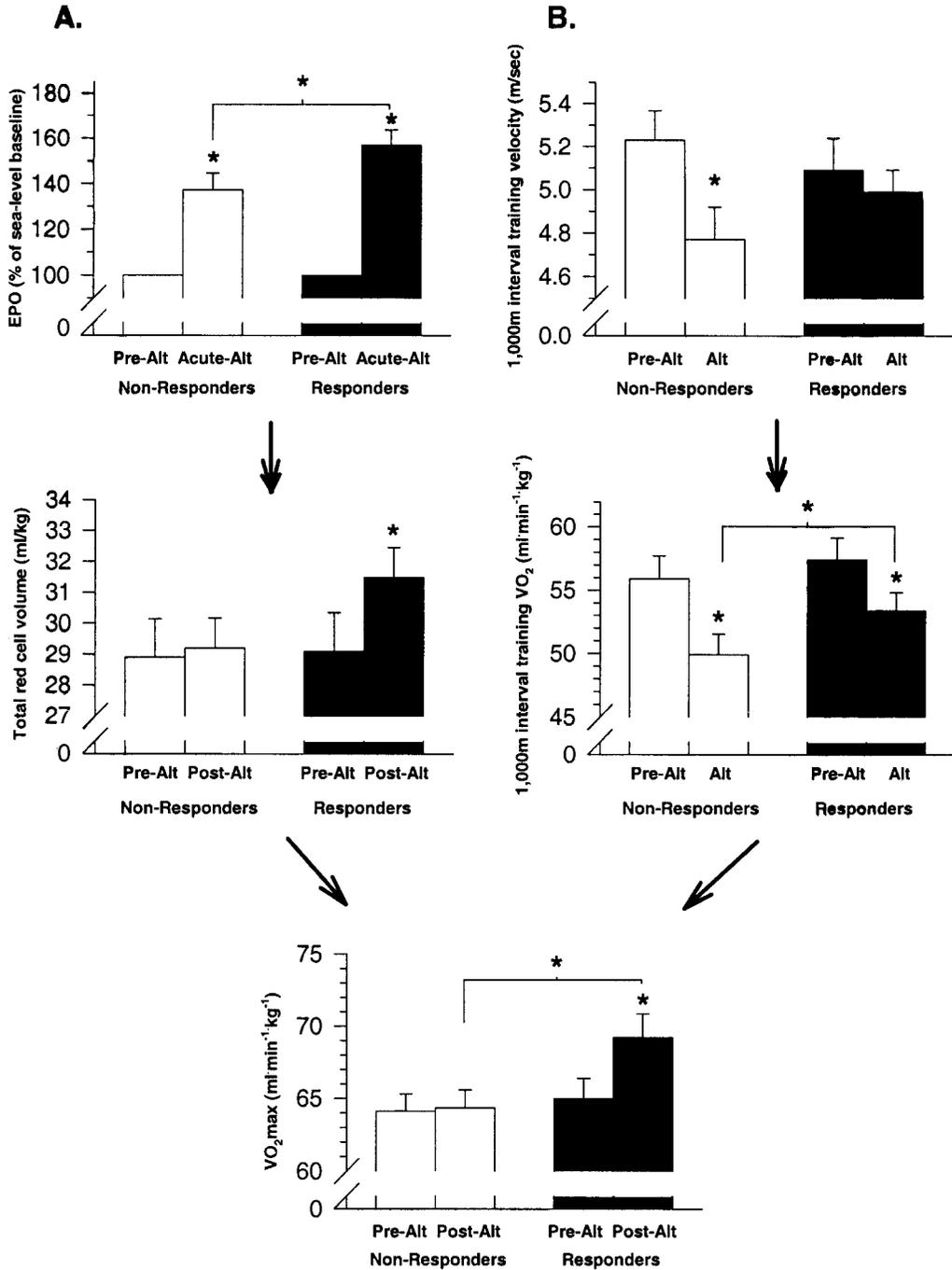A few small studies have been reported in competitive athletes examining the effects of

FIG. 8. Erythropoietic (left) and training (pathways) leading to an increase in $V_{O_{2max}}$ and performance. From Chapman et al., 1998.

hypoxic exercise with mixed results. For example, Banister and Woo (1978) performed high-intensity interval training in elite athletes while breathing 12% O_2 and reported an increase in both aerobic power and anaerobic capacity. In contrast, Vallier et al. (1996) found no significant differences in $V_{O_{2max}}$ or maximal power output in five elite triathletes following intermittent hypoxic training (4000 m). Terrados et al. (1988) investigated the effect of intermittent hypoxic training in eight elite cyclists, randomly assigned to either hypobaric hypoxia (2300 m) or normoxia (sea level), and found no difference between groups for either work capacity or maximal power output at sea level. Most recently, Meeuwsen et al. (2001) evaluated the efficacy of intermittent hypoxic training in a larger

number of triathletes ($n = 16$). Eight trained in a hypobaric chamber at a simulated altitude of 2500 m, whereas eight fitness-matched controls trained at sea level. Again, no significant differences between groups were found following the first posttest conducted 2 d after the training period. However, a second test, conducted 9 d after the training period, revealed significant differences between groups in both maximal power output as measured during an incremental maximal cycle ergometer test and mean and peak power as measured during a Wingate test. No significant differences in $V_{O_{2max}}$ were found. Unfortunately, the training was not controlled during this intermediate period, limiting the strength of the conclusion. Most recently, Truijens et al. (2002) have performed a carefully controlled study in 16 highly trained swimmers comparing high-intensity training in a swim flume under normoxic versus hypoxic conditions in a randomized, double-blind, placebo-controlled design. Although both groups of athletes improved performance (100 and 400 m freestyle) and $V_{O_{2max}}$, they were unable to demonstrate any differences between groups. Moreover, neither swimming economy nor anaerobic capacity improved with this training.

In summary, previous work in both untrained subjects and well-trained athletes has not demonstrated convincingly an additive effect of hypoxia superimposed on endurance training, at least during whole-body exercise. Upon careful reflection, this outcome should not be surprising. Although hypoxic exercise may feel harder, athletes of many different types self-select work rates that are significantly less during hypoxic exercise compared to normoxic exercise (Levine et al., 1992; Levine and Stray-Gundersen, 1997; Brosnan et al., 2000). Thus the power output generated by the muscle is less, and the stimulus for muscle hypertrophy and myosin synthesis must be equivalently less. Moreover, although submaximal heart rates and lactates are higher during hypoxic exercise compared to normoxic exercise, maximal heart rate, cardiac output, and peak lactate during high-intensity exercise are reduced (Sutton et al., 1988, 1992; Cymerman et al., 1989; Hochachka, 1989; Reeves et al., 1990, 1991, 1992; Reeves, 1999), arguing that

neither the cardiovascular system nor the metabolic state of skeletal muscle are "stressed" to a greater degree (McClelland et al., 1998).

In addition, because maximal oxygen uptake is reduced during hypoxic exercise (Buskirk et al., 1967; Faulkner et al., 1968; Terrados et al., 1985; Gore et al., 1997), oxygen flux through skeletal muscle during high-intensity exercise is also reduced. The concept of symmorphosis, as elaborated by Hoppeler and Weibel (1998), argues that for any system, such as the respiratory chain for oxygen transport, the maximal capacity of each parameter is adjusted quantitatively to match the structural and functional limits of the demands placed on the system as a whole. Thus, for the "elite athletes" of the animal kingdom, each step of the pathway of oxygen from the atmosphere to the mitochondria has evolved toward optimal function and maximal aerobic power. According to this principle then, the reduced oxygen flux associated with training under hypoxic conditions would be more likely to lead to downregulation of muscle structure and function associated with reduced oxygen transport, rather than upregulation, as is hypothesized by proponents of hypoxic exercise as the key component of altitude training.

Finally, although some investigators have hypothesized that restoration of normoxia during recovery from exercise could be important for maximizing the rate of protein synthesis, this construct is untenable. Human skeletal muscle has an extraordinary adaptive range of blood flow response and is capable of augmenting flow by nearly two orders of magnitude during maximal exercise (Richardson et al., 1993). At rest, after acclimatization, simple calculations suggest that less than a 10% increase in muscle blood flow (<1 mL/min/100 g) would be required to convey normal oxygen delivery to resting skeletal muscle, even at altitudes up to 3000 m. Moreover, this process of regulating muscle blood flow to oxygen requirements is extremely tightly regulated (Rowell et al., 1986; Ellsworth et al., 1995; Grassi et al., 1996), making it unlikely that there is ever an oxygen lack to *resting* skeletal muscle except under conditions of extreme hypoxia. It is possible, however, that at relatively higher altitudes (i.e., ≥ 3000 m) acclimatization may lead to appetite

suppression, inhibition of protein synthesis, muscle wasting, excessive ventilatory work, and metabolic compensation that is not advantageous for a competitive athlete. In this regard, recent reports by Levine and Stray-Gundersen suggest that there may be a very narrow range of successful performance enhancement with high–low altitude training: altitudes <1600 m may be too low to stimulate an effective erythropoietic response (Ri-Li et al., 2002), while altitudes >3000 m may be complicated by negative aspects of altitude acclimatization that are sufficient to impair performance of highly trained athletes (Witkowski et al., 2001).

Humans are somewhat different though from more athletic animal species in a number of important ways. First, unlike horses or greyhounds, humans have a mass-specific mitochondrial oxidative capacity that is greatly in excess of systemic oxygen transport capacity (Hoppeler et al., 1998). Although at least some of this difference is related to bipedal locomotion, small increases in mitochondrial structure and function are less likely to lead to increases in maximal oxygen transport than increases in oxygen availability. Moreover, elite human athletes living and training at sea level are unable to develop similar levels of circulating hemoglobin–red cell mass as are "high-endurance" animal species that have the ability to autotransfuse by splenic contraction (Kraan et al., 1978). Thus increases in red cell mass and maximal oxygen transport are more likely to lead to improved performance in human athletes than are small changes in muscle structure or function.

In summary, intermittent hypoxic training involving periods of induced hypoxia at rest (such as living high–training low and all its permutations) is a promising technique for enhancing athletic performance without resorting to illegal or unethical methods, such as blood doping or injection of erythropoietin or EPO-derived drugs. However, performing hypoxic exercise by itself without acclimatization is certainly not beneficial for nonathletes and does not seem to be beneficial for competitive athletes, at least under conditions of whole-body exercise. The most likely benefit from hypoxia at rest is to stimulate erythropoiesis, though the "dose" of hypoxia required to induce and sustain this effect remains uncertain and is likely different among individuals based on genetic and physiologic variability.

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