The following letters are in response to the Point:Counterpoint series “Positive effects of intermittent hypoxia (live high:train low) on exercise performance are not mediated primarily by augmented red cell volume” that appeared in the November issue (vol. 99: 2056–2061, 2005; http://jap.physiology.org/content/vol99/issue5).

To the Editor: Each explanation of any phenomenon, biological or other, is model dependant. The common model presumed by all the participants in this debate has been termed the Cardiovascular/Anaerobic/Catastrophic Model of Exercise Physiology (3, 4). The assumption of this model is that it is possible to reduce human exercise performance to one or two “limiting” variables, specifically those involved in the transport to and uptake of oxygen by the exercising muscles. The focus of this discourse between fellow reductionists is the role of the red cell mass as that limiting variable (2). The reasons why this crude model cannot be correct and hence why any conclusions based on it must be simplistic, have been argued elsewhere (3, 4). An alternate model that places the brain at the center of this regulation and for which there is accumulating evidence (1, 4, 5), has been proposed.

The real question inviting a more relevant debate is what changes in which sensory biological signals allow the brains of altitude-conditioned athletes to increase the number of motor units recruited in their exercising muscles and therefore to run faster after living high and training low? Or is it purely a logical or other, is model dependant. The common model based on it must be simplistic, have been argued elsewhere (3, 4). An alternate model that places the brain at the center of this regulation and for which there is accumulating evidence (1, 4, 5), has been proposed.

The real question inviting a more relevant debate is what changes in which sensory biological signals allow the brains of altitude-conditioned athletes to increase the number of motor units recruited in their exercising muscles and therefore to run faster after living high and training low? Or is it purely a placebo effect in athletes who have become mentally conditioned, through saturation exposure to lay and scientific publications, to believe that living high and training low must increase their performance (because all the science proves that Rp and Fp are the ratios of RQ and Rp to the overall resistance to O2 transport. FQ and Fp were estimated from observed changes of VO2max and the accompanying changes of RQ and Rp and amounted to 0.70 and 0.30 for exercises with large muscle groups at sea level (4). Thus, downstream from the lung, the major (70%) limiting factor is O2 transport by the circulation. We estimated ∆RQ/RQ from (2, 5) (assuming unchanged maximal cardiac output): it amounted to ~0.075. Inasmuch as FQ = 0.70, in the absence of any peripheral effects of hypoxia (∆Rp/Rp = 0), this would increase VO2max by 0.055. However, VO2max increased only about half as much (0.03). This smaller increase can be attributed to the negative effects of hypoxia on peripheral O2 use (1). The corresponding increase of Rp (estimated assuming Fp = 0.30) amounts to +0.08.

REFERENCES


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To the Editor: Our view on the issue at stake (3) is that the negative effects of hypoxia on peripheral oxygen use after Hi-Lo offset partially the increase of VO2max predicted on the basis of the augmented hemoglobin concentration ([Hb]). We estimated the relative role of the factors limiting VO2max as follows (4). Two main resistances to O2 transport downstream from the lung are identified: RQ, inversely proportional to the product of maximal cardiac output and [Hb] and Rp, inversely proportional to mitochondrial oxidative capacity and tissue capillarization. The following equation is obtained: VO2max

VO2max’ = 1 + FQ · ∆RQ/RQ + Fp · ∆Rp/Rp;

where VO2max and VO2max’ are the values before or after any given manipulation; FQ and Fp are the ratios of RQ and Rp to the overall resistance to O2 transport. FQ and Fp were estimated from observed changes of VO2max and the accompanying changes of RQ and Rp and amounted to 0.70 and 0.30 for exercises with large muscle groups at sea level (4). Thus, downstream from the lung, the major (70%) limiting factor is O2 transport by the circulation. We estimated ∆RQ/RQ from (2, 5) (assuming unchanged maximal cardiac output): it amounted to ~0.075. Inasmuch as FQ = 0.70, in the absence of any peripheral effects of hypoxia (∆Rp/Rp = 0), this would increase VO2max by 0.055. However, VO2max increased only about half as much (0.03). This smaller increase can be attributed to the negative effects of hypoxia on peripheral O2 use (1). The corresponding increase of Rp (estimated assuming Fp = 0.30) amounts to +0.08.

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To the Editor: Concerning the interesting Point:Counterpoint on the “live high:train low” hypothesis (2), we suggest that during the process of adaptation to hypoxia there would be more things than red cell volume changes. We reported that rats adapted to hypoxia, either by exposure to high altitude (4,340 m, P02 = 61.3 kPa; 1) or to life in a hypobaric chamber (P02 = 53.8 kPa; 4), showed an increase of ~60% in heart mitochondrial nitric oxide synthase (mtNOS) activity and expression. The effect was selective: cytochrome content and several mitochondrial enzymatic activities were unchanged. The NO produced by mtNOS restricts cytochrome oxidase (1)

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normoxic-anoxic transition and extends the oxygenation distance from the blood vessel. The NO-augmented situation would be associated with more areas having enough ATP to sustain a homogeneous and synchronic myofibril contraction. Interestingly, adapted rats showing mtNOS upregulation exhibited better papillary muscle contractility parameters than their control siblings (4). This property may be associated with higher systolic pressure during the cardiac cycle, useful to counteract the increased blood viscosity due to higher RBCV. Hematocrit and mtNOS activity of rats living at high altitude correlated linearly ($r^2 = 0.89; P < 0.001$), suggesting that both components of the adaptation to hypoxia may have common signaling pathways in which HIF-1α plays a central role (3).

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To the Editor: In their desire to align themselves with an accomplished scientist Robert Koch, the supporters (2) have unwittingly highlighted major flaws in the foundation of their self-built “hypoxic castle.” It is noteworthy they have not scrutinized their data for correlations to support (or not) their contention of meeting Koch’s first postulate. They resorted to substituting a different intervention (high altitude correlated linearly ($r^2 = 0.89; P < 0.001$), suggesting that both components of the adaptation to hypoxia may have common signaling pathways in which HIF-1α plays a central role (3).

Fundamental scientific principles, not the least of which is a need to discount the possibility of a placebo effect, have been neglected. Plausible explanations such as changes in economy have been ignored. I am not sure that Koch would view such an abrogation favorably.

REFERENCES


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To the Editor: Levine and Stray-Gundersen (1) propose that augmented red cell volume is the primary mechanism by which a “live high: train low” regimen leads to enhanced athletic performance. Gore and Hopkins (1) question the data leading to this conclusion and propose that other mechanisms, particularly improved exercise economy resulting from changes within muscle cells may contribute to the effect.

Missing from this debate has been a consideration of possible changes in microvascular structure associated with intermittent hypoxia. Capillary density is a key parameter influencing oxygen delivery to muscle, because the distance that oxygen can diffuse into oxygen-consuming tissue is very short. Theoretical simulations of oxygen diffusion in skeletal muscle (3) based on published values of capillary density show that a substantial fraction of tissue is hypoxic even at submaximal rates of oxygen consumption. Such conditions would be expected to lead to heterogeneous levels of metabolic activity and force generation within and among muscle fibers. Increases in capillary density would lead not only to increased VO2 max but also to more uniform tissue oxygenation in submaximal exercise. Such a change might improve exercise economy even without changes in muscle cell properties.

Hypoxia is frequently implicated as a cause of vascular growth and proliferation. Lundby et al. (2) found no increase in muscle capillary density when subjects were exposed to 2 or 8 wk of acclimatization at 4,100 m. However, it is tempting to speculate that the combination of growth stimuli resulting from a live high:train low regimen would be effective in increasing capillary density. This, along with any effects of increased red cell volume, could contribute to improved exercise performance.

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To the Editor: Hochachka et al. (2) suggested that exposure to hypoxia is likely to elicit adaptations all along the oxygen transport and utilization cascade. Therefore, multiple loci of adaptations arise, improving maximal oxygen uptake and/or more qualitative aspects of energy production and use. On one side, Levine and Stray-Gundersen report performance gains after 12-16 h/day of hypoxia at rest, via increased red cell volume (RCV) and \( V\dot{O}_2\max \). On the other side, Gore and Hopkins observed performance improvement after shorter hypoxia exposure (~8 h/day), involving no \( V\dot{O}_2\max \)-mediated mechanisms (3). Recently, our group gathered evidence that coupling short hypoxia exposure with intense exercise in trained runners improved aerobic performance capacity together with \( V\dot{O}_2\max \) (2), despite unchanged RCV. As maximal cardiovascular response was considered already optimal in our athletes, their increased maximal oxygen pulse suggested that peripheral oxygen extraction rather than oxygen delivery increased (1). Accordingly, molecular and cellular data suggested an improved pH regulation and a qualitatively enhanced mitochondrial function (4), thereby allowing more efficient aerobic energy production and distribution within myocytes. Altogether, observations from many groups show that hypoxia exposure induced adaptations that encompass distinct biological systems, all controlling limiting steps of \( V\dot{O}_2\max \) and/or other determinants of endurance performance, depending on its modality. Consequently, in addition to its erythropoietic pathways, the metabolic stress provided by intermittent hypoxia at rest and/or exercise could elicit alternative physiological adaptations, especially if hypoxia duration is limited to permit higher training loads. Interestingly, combining hypoxia with exercise may further reduce the hypoxia duration needed to improve aerobic performance, the ultimate goal of athletes.

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To the Editor: An increased red cell volume (RCV) is believed to be the predominant factor of the improvements in \( V\dot{O}_2\max \) and exercise performance in response to “living high:training low” (3). The following lines attempt to convince the reader that an increase in RCV with acclimatization may offer additional advantages for exercise performance.

Among the three mechanisms that govern the movement of lactate across the erythrocyte membrane, the lactate-H+ co-transport via the monocarboxylate transporter 1 (MCT1) constitutes the primary pathway. The fivefold increase in the MCT1 content of purified erythrocyte membrane fractions observed after an 8-wk sojourn at 3,700-4,100 m (2) indicates that altitude acclimatization improves the transport capacity for lactate and H+ across the erythrocyte membrane. Furthermore, the increase in the RCV with acclimatization (2, 3) enhances the dilution space for lactate and protons released in the plasma by the exercising muscles (1, 4). Taken together, these adaptations in response to altitude acclimatization enhance the capacity of the erythrocytes to pick up lactate and protons from the plasma. A rapid and substantial storage in erythrocytes during exercise may reduce the lactate and H+ accumulations in the plasma, increase the muscle-to-blood lactate and protons gradients and in fine favor the net release of these ions from the active muscles (1, 2, 4). In view of the importance of lactate exchange ability on human performance during high-intensity exercise (5), the potential role of the increase in RCV with altitude acclimatization on the lactate and H+ transport processes deserved to be mentioned.

REFERENCES


Point: Counterpoint Comments

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To the Editor: In a previous study (1) we observed that $V_O_2_{max}$ of rats living and training in normoxia for 4 wk was improved by 10 additional days of living in hypoxia ($P_{O_2}$, 70 Torr) and training in normoxia (LHTL) compared with rats that continued to live and train in normoxia (LLTL). Both groups trained at equal exercise intensity. The higher $V_O_2_{max}$ of LHTL was due to elevated arterial blood $O_2$ content secondary to hypoxia-induced polycythemia. This, in the presence of similar cardiac outputs, resulted in enhanced tissue $O_2$ delivery ($Q_{O_2_{max}}$) in LHTL over LLTL. Interestingly, the effect of elevated $Q_{O_2_{max}}$ was partially offset by a lower tissue $O_2$ extraction ratio ($O_2$ER) in LHTL. $O_2$ER is determined by the ratio of diffusive-to-perfusional tissue $O_2$ conductances (3). Tissue $O_2$ diffusing capacity, estimated from $V_O_2_{max}$ and mean tissue capillary $P_{O_2}$, was similar in LHTL and LLTL. On the other hand, the higher blood $Hb$ concentration in LHTL increased perfusional $O_2$ conductance, which would tend to reduce $O_2$ER. These results support the idea that polycythemia contributes to the improved exercise capacity in animals living in hypoxia and training in normoxia (2). However, polycythemia can be a self-limiting mechanism of $V_O_2_{max}$ enhancement due to its opposing effects on $Q_{O_2_{max}}$ and on $O_2$ER. Furthermore, as severity of hypoxia increases, additional negative effects of acclimatization to hypoxia—reduced maximal heart rate and cardiac output, pulmonary hypertension, and reduced tissue oxidative enzyme activity—may tilt the balance against the effect of augmented blood $O_2$ levels.

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To the Editor: We read with great interest the excellent Point: Counterpoint article in the Journal of Applied Physiology on the hypothesis that intermittent hypoxia is mediated only by augmenting red cell volume (3). As outlined in this article, the transcription factor hypoxia inducible factor 1 (HIF-1) plays a central role in adaptation to hypoxia. In fact, during conditions of hypoxia, HIF-1α is stabilized and dimerizes with HIF-1β, followed by translocation into the nucleus and binding to specific DNA sequences within the promoter region of hypoxia inducible genes. The promoter region of the erythropoietin gene contains such an HIF-1 binding site. Therefore, hypoxia is associated with transcriptional induction of erythropoietin, leading to an increase in red cell volume (4). However, multiple studies have revealed that HIF-1 is not only a regulator of erythropoiesis, but also central to regulation of angiogenesis, metabolism, vascular function, and inflammation. For example, recent studies demonstrated a central role of adenosine as extracellular signaling molecule in maintaining vascular barrier function during hypoxia (1). In fact, mice lacking the HIF-1-dependent pacemaker enzyme in extracellular adenosine generation (CD73) develop profound vascular leakage and excessive neutrophil tissue infiltration during hypoxia (5). Moreover, other recent studies have identified oxygen-independent activation of HIF-1 by inflammation and infection (2). Due to the high complexity of the HIF-1 system, including multiple input and output variables that have recently been identified, we think it is critically important to consider multiple consequences of HIF-1 activation to understand effects of intermittent hypoxia on exercise performance.

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To the Editor: To me, red cell volume (RCV) refers to the volume of individual cells. Red cell volume increases in virtually all hypoxic vertebrates (3) as a consequence of oxygen-induced changes in ion and water transport (1). Both the increase in cell volume and the associated increase in in-
traerythrocytic pH contribute to an increased haemoglobin-oxygen affinity, also observed in hypoxic mammals at altitudes above ~4,500 m. However, because the oxygen-dependent changes in ion transport appear and disappear immediately on changes in oxygen tension, the living high:training low (LHTL) effects on the efficiency of oxygen transport cannot be caused by such changes in RCV.

Clearly, Levine and Stray-Gundersen (2) use the phrase “augmented red cell volume” to indicate an increase in the total number of erythrocytes in blood. In their view, the improved performance after LHTL is brought about by erythropoiesis. Even intermittent hypoxia accelerates the production of erythropoietin and stimulates erythropoiesis (5). Despite this, it is difficult to show conclusively that changes in performance/muscle function would be caused by the production of new erythrocytes, because changes in plasma volume occur rapidly during altitude to sea level transfer (4). Furthermore, I am not aware of measurements of red cell flux through the capillaries of working muscles in LHTL. Before such measurements are available, and show differences related to erythropoietic activity, it is also feasible that the beneficial effects of LHTL are due to other modifications of capillary oxygen flux in working muscles.

REFERENCES


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To the Editor: Recurrent episodes of hypoxia, which are indicative of the “live high:train low” (LHTL) method of altitude training, clearly have the ability to improve exercise performance via an increase in RCV/Hb\textsubscript{mass} (3, 5). It seems clear from the literature that if the hypoxic stress is great enough, hypoxic-inducible factor-1α (HIF-1α) stabilization will invoke erythropoiesis, in turn enhancing oxygen delivery capacity. It also seems possible that other mechanisms related to more efficient use of oxygen may be involved (3). However, the performance-mediated adaptation suggested by Gore and Hopkins of improved economy is unlikely to be a “plausible alternative” to hematological adjustments, but rather a contributor to improvements in performance. Equally, the amount of evidence supporting hypoxic-induced increases in RBV/Hb\textsubscript{mass} should not be ignored.

The delivery of oxygen from the environment to the working muscle is complex. Other mechanisms that could, in part, explain performance improvements mediated by both enhanced oxygen delivery and utilization include augmented concentrations of 2,3-DPG; increased blood-pulmonary transit times, which is consistent with some of the studies where improved economy and a reduced submaximal heart rate have been witnessed [for references, see Counterpoint, Ref. 3]; arterial and capillary remodeling [pulmonary (2) and systemic (4)]; mitochondrial adjustments; and increases in oxidative enzyme activity and buffering capacity (1). With so many mechanisms involved in oxygen availability/utilization, can performance increases be purely attributed to one physiological adjustment?

In conclusion, more research is needed that develops a mechanistic approach to understanding the effects of LHTL on the above adaptations and their relationship to performance.

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conductance in the lungs and/or muscles [but reduce the ratio of diffusional to perfusional conductances (4)], it is not surprising that interventional studies show variable effects of RCV and/or plasma volume change on overall performance (1, 5). Levine and Stray-Gundersen may have shown RCV differences and even correlation with performance, but they have not established cause and effect.

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To the Editor: The clear way to verify the point that “live high:train low” (LHTL) effects are derived primarily by augmented red cell volume (RCV) (2) would be just to state the correlation between changes in RCV and performance enhancement after LHTL, as mentioned in the counterpoint by Gore and Hopkins (2), because we realize that VO\textsubscript{2 max} is not good as the sole criterion to judge the efficacy of high-altitude exercise training programs (1). In fact, in the high-altitude training program, the improved VO\textsubscript{2 max} was not associated with enhanced exercise performance in live high:train high subjects (3) or exercise performance increased without the improvement of VO\textsubscript{2 max} (4).

At the same time, it is important to see in the relationship between the two parameters if augmented RCV is “necessary” to enhance exercise performance after LHTL. Probably, LHTL might give athletes a variety of physiological adaptations in muscle metabolism, structure, and fiber type composition, which are related to exercise economy. Mostly these factors show such large interindividual differences as well as other physiological factors including blood parameters, that the correlation between the two parameters may be statistically non-significant. Although, in such cases, if LHTL subjects who improve their exercise performance show augmented RCV, it could be a necessary condition to enhance exercise performance. In fact, most LHTL subjects showed even or increased performance level except for one subject in Fig. 6 (3), thus their changes in RCV (increase or not) would reveal the necessity of the augmented RCV in LHTL effects.

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To the Editor: Although the living high:training low model has been demonstrated to improve endurance performance (3), its mechanisms seem to be unclear. Long-term exposure to hypoxia raises erythrocyte volume and hematocrit (5), leading to an increase in oxygen delivery. However, Wolfel et al. (6) demonstrated that total body and leg oxygen delivery remained unchanged despite an increase in hemoglobin concentration and arterial oxygen saturation after acclimatization to high altitude. According to their study, after acclimatization at 4,300 m, exercise cardiac output decreased 25% and leg blood flow decreased 18% compared with arrival (6). Hypoxia-induced polycythemia leads to increase systemic vascular resistance, resulting in fall in both cardiac output and blood flow, offsetting the increase of erythrocyte. Therefore, positive effects of LHTL on exercise performance would be not mediated primarily by augmented red cell volume (2). One of other mechanisms to explain the effects of LHTL might be hypoxia-induced vascular remodeling. Chronic hypoxia causes both angiogenesis and vascular dilatation in the brain (4) and skeletal muscles (1). The increase in blood vessels of the rat brain induced by hypoxia persisted for a while after the termination of hypoxia (4). This vascular adaptation to hypoxia could increase oxygen conductance to the tissues and, consequently, improve exercise economy and performance. Further studies are needed to elucidate the mechanisms of LHTL effects.

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To the Editor: The title of the discussion (5) suggests a proven effect of “live high:train low” on sea level performance. The evidence presented by Levine and Stray-Gundersen is based mainly on one controlled study (4) that has, however, weaknesses. The live high:train low group trained at a possibly still effective altitude (1,250 m), the controls at sea level. Responders and nonresponders differed in training intensity (3). Gore and Hopkins assume a placebo effect as factor for performance improvements. Interestingly an altitude sojourn reduces the blood concentration of ammonia, a substance suggested as a cause of fatigue (see Ref. 2). In addition, no thresholds are reliable because of long-lasting changes in ventilatory stimulation and blood lactate levels (see Ref. 2).

Both groups emphasize the importance of hemoglobin mass or red cell volume for performance more than that of hemoglobin concentration. Indeed hemoglobin concentration normalizes within days after return from altitude by hemodilution (2). The after-effect of altitude is similar to that of conventional endurance training: increase of both red cell and plasma volumes without rise in hemoglobin concentration. This avoids viscosity problems. Natural “blood dopers,” like horses that inject erythrocytes stored in their spleen into the circulation do not suffer from this complication. Their erythrocytes are tiny [cell volume 36 fl (1)], reducing resistance in small vessels. In humans, blood volume increases, favoring filling of the heart, seem to be more important for training (and doping?) effects on sea level performance than hemoglobin concentration changes.

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To the Editor: Although the “living high:training low” (LHTL) model has been demonstrated by different research groups to be effective for increasing athletes’ abilities, the mechanisms underlying the improved endurance capacity reported after LHTL hypoxic exposure has received much scientific enquiry. Levine and Stray-Gundersen (4), in their rebuttal, presumed that the positive effects of LHTL on exercise performance are
mediated primarily by augmented red cell volume (RCV) and \( \text{VO}_2\text{max} \) resulted from hypoxia-inducible erythropoietin (EPO) expression. They should not have been so cavalier in declaring that “there are no other effects of altitude acclimatization that can be manipulated independently and demonstrated to improve athletic performance over a sustained period of time.” Other studies indicate that the hypoxia-induced performance improvement may be due to upregulation of skeletal muscle metabolism (1) and reduction of whole body oxygen utilization (2) rather than changes in hematological variables and \( \text{O}_2 \) delivery.

Adaptation to hypoxic environment in high altitude switches on a regulatory system involving various intracellular changes mediated by hypoxia-inducible factor-I (HIF-1) in most cells. HIF-1 acts as a master regulator of a series of hypoxia-regulated gene expression. HIF-1 target genes are particularly relevant to cancer encoding angiogenic factors, proliferation/survival factors, glucose transporters, and glycolytic enzymes, thus a key factor involving hypoxia responsible erythropoiesis, angiogenesis, glucose metabolism, and iron metabolism (3), all of which are plausible factors leading to performance improvement after hypoxic exposure. Indeed, the published data are still far from sufficient to elucidate the mechanisms of the positive effect of LHTL on performance. In my opinion, HIF-1 seems more likely the central component than increases in RCV.

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To the Editor: I read with great interest the Point:Counterpoint “Positive effects of intermittent hypoxia (live high:train low) on exercise performance are/are not mediated by augmented red cell volume” (RCV, 3). Maximal oxygen uptake (\( \text{VO}_2\text{max} \)) is obviously an important variable in regard to endurance performance. Therefore, if RCV increases after a live high: train low protocol, endurance performance would improve due to an increased \( \text{VO}_2\text{max} \). In addition, exercise economy is also known as one of the variables for determining performance. Levine and Stray-Gundersen’s study (3) and others did not find any changes in exercise economy after hypoxic exposure, whereas studies from other independent laboratories showed an improvement of exercise economy after chronic or intermittent hypoxic exposure (1, 2, 4), as Gore and Hopkins (3) mentioned. Thus it seems reasonable to suppose that, in some cases, hypoxic interventions improve exercise efficiency and that an increased RCV during hypoxic exposure might not be the definitive mechanism to improve endurance performance. However, a major limitation of endurance performance studies after live high:train low protocols has been the lack of a placebo group with the same expectations of an improvement of performance as the experimental group. This is a concern because of the volitional nature of endurance performance tests. To my knowledge, no study of performance after a live high:train low protocol has included a placebo group. Therefore, I suggest that future studies of this question incorporate placebo groups in their design.

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To the Editor: A physiological adaptable range enables accommodation to differing external environments and stressors that challenge homeostasis. Implicit within this concept are lower and upper limits, beyond which pathophysiological processes supervene. \( \text{VO}_2\text{max} \) effectively marks an athlete’s upper physiological threshold for oxidative metabolism and thus also marks the lactate threshold (when oxygen becomes limiting) and muscular performance declines. Inasmuch as \( \text{Hb}\%\text{sat} \) is >99% at sea level, increasing absolute volume delivery of oxygen to respiring tissues is desirable (through increased PCV), hence live high:train low. There is considerable evidence to support this training program (2). However, each system has limits, and increased PCV increases blood viscosity, reduces erythrocyte capillary transit time (overtraining), and limits performance. The UCI arbitrarily defines a PCV of >50% as evidence of blood doping and imposes a ban. As many athletes compete near this cut-off they must engage other physiological mechanisms to delay the onset of anaerobic metabolism. Of the many, improved exercise efficiency or muscular economy at a fixed work output offers the potentially greatest majority benefit. Indeed, physiological evidence suggests improved exercise efficiency/economy as key to the achievements of the most accomplished athlete of the modern era, Lance Armstrong (1). In conclusion, my point is this: to pigeon-hole improvements in performance after “living high: training low” as due entirely to increased PCV or to improved
exercise economy does not fully appreciate the range of adaptations that are made and the interrelationships that exist between them.

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To the Editor: Increased red cell volume (RCV) is one possible adaptation to altitude training, but other factors such as exercise economy are also important in enhancing endurance performance. We observed a 3.3% improvement in running economy (RE) after 20-day moderate simulated live high:train low (LHTL) altitude exposure in 10 elite distance runners without any change in hemoglobin mass (Hbmax) and improved competitive performance after the exposure (5). This study and others have shown that improvements in performance can be obtained without changes in RCV.

Error of measurement in RCV is a pertinent issue and cannot be easily dismissed as suggested by Levine and Stray-Gundersen (4). Clearly there is wide variation in the reliability of quantifying RCV depending on the technique (1). The reliability of measures ranges from 1.7% for the Burge and Skinner carbon monoxide (CO) rebreathing method, ~4% for other CO rebreathing methods, to 6.7% for the Evans blue dye method (1). Given the reported increase of 7% in RCV after altitude training (3), the magnitude of typical error for the Evans blue method (6.7%) makes it less likely this method can be used to confidently identify meaningful changes. Finally Levine and Stray-Gundersen’s contention (4) that results of the Evans blue and CO rebreathing methods are “virtually identical” cannot easily be accepted given that the estimates of the Evans blue method typically return RCV ~10% higher than the CO rebreathing technique as highlighted in Ref. 2.

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To the Editor: We congratulate Drs. Levine and Stray-Gundersen and Gore and Hopkins (3) for an excellent Point: Counterpoint of the live high:train low (LHTL) concept. LHTL, inspired by the work of Daniels and Oldridge (2) in response to studies performed around the 1968 Olympics, presents a well-accepted protocol regarding the use of altitude to prepare for sea level performance. Levine and Stray-Gundersen are compelling in their defense of the hypothesis that LHTL is primarily mediated by increases in red cell volume (RCV). Gore and Hopkins effectively argue that factors other than the increase in RCV that occurs in many individuals (responders) with altitude exposure must be considered. A generation ago, Terrados et al. (4) demonstrated that there were unique physiological responses to altitude training that might explain at least part of the demonstrated effects of altitude training. The proposal of increased muscular efficiency by Gore and Hopkins as a non-RCV mediator of an ergogenic effect of LHTL seems unlikely, because improvements in muscular efficiency are typically observed after training at intensities approximating VO2max (1). Why living (but not training) at altitude, where the forcing function of hypoxia is small, would promote changes in efficiency during muscular exercise is not at all clear. Given the logistic difficulties of organizing LHTL, it would be of interest to develop quick-response predictors of individuals likely to be responders or nonresponders and to define the dosimetry of the erythropoietic response to altitude, which seems to be the major experimental difference of opinion between the opponents (3, 4).

REFERENCES

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To the Editor: Laboratory investigations, although well designed, cannot predict the athlete performance at sea level (SL) due to errors of physiological methods used and complexity of human performance. Still some athletes may benefit from LHTL, because small variations (i.e., in [Hb]) not detected by statistics may cause important performance changes. The presented $r = 0.51$-0.63 explains only 25–36% of the variation! Individual data may tell us more.

Does the stimulated erythropoiesis (RCM) improve performance? Levine and Stray-Gundersen (3) disregard a basic question. What happens with central circulation after >20 days at altitude? It is known that changes in blood volume with or without variations in [Hb] changes SV and Q during maximal exercise, influencing both $\dot{V}O_2 max$ and performance (1, 2).

Gore and Hopkins trust that an enhanced running economy explained improved SL performance; however, they did not present any physiological background for that (3). It is evident that an improvement in running economy cannot compensate for the reduced training intensity at altitude at return to SL.

An eventually increased performance at SL after LHTL seems not related to factors discussed above. What mechanism(s) would then be responsible for an improvement? One would expect to find at least some differences in morphology, buffer capacity, etc., between world class athletes from highland and SL, but that is not the case (4).

It is not necessary to have a reasonable physiological explanation to explain an experience. But it helps. So the question remains: is performance at SL increased at all after LHTL?

REFERENCES

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