the Journal of Strength and Conditioning Research™

The Effects of Normobaric Hypoxia on the Acute Physiological Responses to Resistance Training: A Narrative Review

Giselle L. Allsopp,[1] Florian A. Britto,[2] Craig R. Wright,[1] and Louise Deldicque[3]

[1]Institute for Physical Activity and Nutrition, School of Exercise and Nutrition Sciences, Deakin University, Victoria, Australia; [2]University of Paris Cité, Institut Cochin, Paris, France; and [3]Institute of Neuroscience, UC Louvain, Louvain-la-Neuve, Belgium

Abstract

Allsopp, GL, Britto, FA, Wright, CR, and Deldicque, L. The effects of normobaric hypoxia on the acute physiological responses to resistance training: a narrative review. *J Strength Cond Res* XX(X): 000–000, 2024—Athletes have used altitude training for many years as a strategy to improve endurance performance. The use of resistance training in simulated altitude (normobaric hypoxia) is a growing strategy that aims to improve the hypertrophy and strength adaptations to training. An increasing breadth of research has characterized the acute physiological responses to resistance training in hypoxia, often with the goal to elucidate the mechanisms by which hypoxia may improve the training adaptations. There is currently no consensus on the overall effectiveness of hypoxic resistance training for strength and hypertrophy adaptations, nor the underlying biochemical pathways involved. There are, however, numerous interesting physiological responses that are amplified by performing resistance training in hypoxia. These include potential changes to the energy system contribution to exercise and alterations to the level of metabolic stress, hormone and cytokine production, autonomic regulation, and other hypoxia-induced cellular pathways. This review describes the foundational exercise physiology underpinning the acute responses to resistance training in normobaric hypoxia, potential applications to clinical populations, including training considerations for athletic populations. The review also presents a summary of the ideal training parameters to promote metabolic stress and associated training adaptations. There are currently many gaps in our understanding of the physiological responses to hypoxic resistance training, partly caused by the infancy of the research field and diversity of hypoxic and training parameters.

Key Words: altitude, strength training, exercise physiology, exercise metabolism

Introduction

Altitude training is a long-standing strategy used by endurance athletes to improve their aerobic capacity. Advances in technology led to the creation of a manmade hypoxic environment, where the air pressure remains similar to sea level, although the fraction of inspired O_2 (FiO_2) is reduced (termed normobaric hypoxia). The use of normobaric hypoxia has become popular at training centers and is now used for a wider variety of training outcomes such as muscle hypertrophy and strength. There is growing interest in the potential benefits of performing resistance exercise in normobaric hypoxia (37,48,95).

There are now at least 16 studies examining the chronic training adaptations to resistance exercise in normobaric hypoxia. A number of these studies reported that hypoxia increases the magnitude of training adaptations to a greater extent than normoxic training, including skeletal muscle hypertrophy (70), strength (45), strength endurance (53), and even aerobic capacity (61). Although a systematic review and meta-analysis concluded that hypoxic resistance training did not consistently enhance training adaptations compared with normoxia, they agreed that with the optimal training variables, hypoxia is a promising method to enhance the training outcomes from resistance exercise (79).

Address correspondence to Giselle L. Allsopp, g.allsopp@deakin.edu.au.

Journal of Strength and Conditioning Research 00(00)/1–11

Several studies examined the acute physiological responses to a single bout of resistance training in hypoxia. Some of these studies aimed to elucidate the mechanisms by which hypoxia may enhance skeletal muscle hypertrophy, whereas others focused on the metabolic and hormonal responses to hypoxic training. Some intriguing responses have been characterized, including a greater growth hormone response to resistance training in hypoxia (56) and the potential modulation of satellite cell–dependent hypertrophy pathways such as myoblast determination factor 1 (MyoD), myogenic regulatory factor 4 (MRF4), and myogenic factor 5 (Myf5) (95). There is evidence that hypoxia increases the metabolic stress response to resistance exercise, including greater disturbances to acid-base balance and increased postexercise oxygen consumption (77). Currently, the mechanisms underpinning the adaptations to hypoxic training are not fully clear, and there is still much to learn about the acute physiological responses to this training method. Despite the infancy of the hypoxic training literature, there is growing interest in the application of this training method to trained populations (45) and clinical populations including older adults (1), individuals with obesity (72), and metabolic disease (83).

This review will outline the acute physiological responses to resistance training in normobaric hypoxia. All key physiological responses in the literature are outlined, including the metabolic, autonomic, hormonal, immune, and skeletal muscle specific responses. The research strategy focuses on human trials that use resistance exercise in intermittent normobaric hypoxia (<6 hours

exposure). Studies using hypobaric hypoxia are not part of the research strategy because of the long periods of exposure to hypoxic conditions where the physiological responses are likely different. Endurance training and high-intensity internal training were not included in the primary research strategy as they were considered outside the scope of the review and have received considerable attention in the literature. Where the literature is limited in relation to resistance training, occasionally the review includes brief discussion of hypoxic training studies that used endurance training and high-intensity interval training (HIT) to draw potential comparisons.

The review will also outline the fundamental exercise physiology underpinning these responses, with the aim of increasing knowledge among applied sport scientists and strength and conditioning specialists. The review will also link the acute physiological responses to the known chronic adaptations to hypoxic training, with particular focus on the potential applications to different populations.

Literature Search Strategy

Key terms used in the literature search included (Resistance OR Strength) AND (Exerc*[Title] OR Train*[Title]) AND (Hypox*[Title] OR Altitude[Title]). Asterisks were used to search for variants of the search terms (e.g., hypoxia vs. hypoxic). An initial selection was made based on the title and language of the articles, where articles written in English were included. After screening the articles, those using normobaric hypoxia and resistance exercise were included in the review. The primary focus of the literature search was on human studies, those using animal models and cell culture were included where human studies were lacking. Because of the narrative review approach, other articles related to systemic hypoxia exposure, endurance exercise, and high-intensity exercise were included where appropriate. Given the different physiological responses to blood flow restriction training compared with systemic hypoxic training (as outlined by (75)), this review focuses on resistance training in normobaric hypoxia. The last search of literature occurred on March 3, 2023.

Oxygen Homeostasis and Hypoxia Exposure

The regulation of oxygen homeostasis is vital for the metabolism of mammalian cells to perform basic human functions including movement and tissue growth (58). Oxygen homeostasis is tightly regulated, where any discrepancy between supply and demand triggers a rapid cellular response to restore adequate oxygen saturation (65). Normobaric hypoxia exposure is typically achieved by nitrogen generators that replace a fraction of the oxygen with nitrogen (4). Normobaric hypoxia, therefore, mimics the local oxygen partial pressure at genuine altitude, where a decrease in the partial pressure gradient of oxygen at the respiratory membrane in the lungs reduces the oxygen supply to the bloodstream.

In normal sea-level conditions (normoxia), arterial oxygen saturation (SpO_2) is approximately ≥98% in healthy individuals. Acute exposure to environmental hypoxia causes a rapid reduction in SpO_2 that recovers quickly after returning to normoxic conditions. The normobaric hypoxic conditions used by the hypoxic training literature range from a FiO_2 of 12.6% (101) to 16.0% O_2 (70), reducing SpO_2 to approximately 80.3 ± 9.1% to 94.0 ± 2.1% (mean ± *SD*), respectively. Although a chronic SpO_2 value in this range would spark concern in a clinical setting, short-term exposure to moderate hypoxia during exercise appears to be well-tolerated by numerous populations including older adults (4) and individuals with type II diabetes (59), obesity (72), and coronary artery disease (11).

Only a few studies used a customized hypoxic dose that used a biofeedback system to maintain a consistent SpO_2 in each subject (61,94). This is an interesting approach with pros and cons. Customizing SpO_2 ensures that the hypoxemia experienced by each individual is consistent, and thus the physiological response to training may be more homogenous compared with a standard hypoxic dose. However, this approach is more time consuming compared with training multiple subjects in a hypoxic chamber set to a standard FiO_2. Irrespective of the hypoxic dose and method of hypoxic delivery, practitioners and researchers using hypoxic protocols should recognize that there is substantial interindividual variability in the physiological response to hypoxia exposure; therefore, there is variability in the responses to hypoxic resistance exercise (refer to review for detail on hypoxic tolerance (20)). Although the SpO_2 responses to hypoxia are somewhat varied among individuals, there are many studies that describe the biochemical pathways that are commonly activated with hypoxic exposure.

Hypoxia-Induced Cellular Pathways

Hypoxia-inducible factor 1 (HIF-1) is a key factor that regulates the downstream cellular responses to low SpO_2. HIF-1 is a transcription factor comprised of a β-subunit and an α-subunit that contains an O_2 dependent degradation (ODD) domain (87). In normoxic conditions, the prolyl-hydroxylase 2 (PHD2) hydroxylates the ODD domain and causes degradation of the α-subunit, ultimately inhibiting HIF-1 protein stabilization (99). In hypoxic conditions, the fall in O_2 causes PHD2 inhibition leading to the stabilization of HIF-1 that subsequently binds to and activates over 1,000 downstream target genes (82). Although it is clear that hypoxic resistance training does not cause a prolonged increase in HIF-1α in peripheral tissues (53), it is likely that HIF-1α is transiently up-regulated during each exercise session in hypoxia. This is evidenced by numerous studies that identified changes in downstream gene targets of HIF-1α with hypoxia exposure including angiogenic, metabolic, and cell survival pathways (23,84,87,88).

The stabilization of HIF-1α during hypoxia promotes the expression of several enzymes regulating glucose uptake and metabolism including glucose transporter 1, hexokinase II, and phosphofructokinase (PFK) (23). Hypoxia activates a key signaling protein called adenosine monophosphate–activated protein kinase (AMPK), which protects cells from sustaining damage through various signaling pathways (39). Adenosine monophosphate–activated protein kinase promotes translocation of vesicles containing GLUT4 to the plasma membrane via the phosphorylation of TBC1 domain family member 1 and TBC1D4 (13), increasing glucose uptake by the tissues under hypoxia. Adenosine monophosphate–activated protein kinase also regulates mitochondrial biogenesis through the activation of peroxisome proliferator–activated receptor-c coactivator-1 alpha (PGC1α) (47).

HIF-1A Pathways During Acute Exercise

The effects of hypoxic resistance exercise on skeletal muscle oxygenation and HIF-1 stabilization are currently unclear.

Generally speaking, blood supply and, therefore, oxygen supply to the muscle is well maintained by the autonomic nervous system (ANS). The vasculature supplying skeletal muscle responds to both exercise and hypoxic conditions to increase blood supply. Hypoxia achieves this by causing compensatory vasodilation of blood vessels (reviewed elsewhere (46)). Muscle oxygenation and the stabilization of HIF-1 are impacted by the severity of the hypoxic exposure and the training parameters. One of the few studies that measured muscle oxygenation during hypoxic exercise used 5×10 repetitions of high-intensity resistance exercise at 70% of 1 repetition maximum (1RM) in FIO_2 13.0% with short interset rest periods (51). Near-infrared spectroscopy analysis of the vastus lateralis showed that the hypoxic group had significantly lower muscle oxygenation compared with the normoxic group (17 vs. 27%). This finding was not replicated by a more recent study that performed 3×10 repetitions of resistance exercise at 60% 1RM in FIO_2 16.0%, where muscle oxygenation was not significantly different between groups (86). Although the slightly higher exercise intensity and set range may have contributed to this response, it appears that a greater level of hypoxia is required to elicit skeletal muscle hypoxemia (70). This is not surprising given that skeletal muscle is relatively resistant to hypoxia (46). Muscle fiber type is also likely to impact the skeletal muscle response to acute hypoxia; however, there is little evidence to support this in the context of resistance exercise.

Gnimassou et al. (31) measured muscle oxygenation during high-intensity resistance exercise (80% 1RM) in FIO_2 14.0% and also measured HIF-1 in skeletal muscle at 15 minutes and 4 hours postexercise. Neither muscle oxygenation nor HIF-1 was different between normoxic and hypoxic-trained groups, possibly because of the relatively long 2-minute interset rest period used. HIF-1 is also hard to quantify because of its short half-life of 5–8 minutes (7) and, therefore, could have somewhat degraded before the first measurement point at 15 minutes postexercise.

Regardless of local muscle oxygenation, there is a robust reduction in SpO_2 during hypoxic resistance exercise (53,56) that likely causes the activation of various HIF-1–regulated pathways including cell survival, metabolism, and angiogenesis. For example, plasma concentrations of vascular endothelial growth factor (VEGF) are significantly up-regulated after 8 weeks of resistance training in FIO_2 14.4% compared with the same training in normoxia (53). VEGF up-regulates skeletal muscle angiogenesis and thus may provide positive metabolic adaptations to resistance training in hypoxia that are not typically present after normoxic resistance training (discussed later in the review).

Skeletal Muscle Specific Responses to Normobaric Hypoxic Resistance Training

Muscle Mass and Strength Adaptations

Repeated bouts of resistance exercise are known to induce changes in skeletal muscle morphology and functional adaptations related to strength and power. Performing resistance exercise in hypoxic conditions may potentiate muscle adaptations usually observed after resistance exercise in normoxia (24). Although improvements in muscle strength have been observed without concomitant hypertrophy, increases in muscle mass are often detected after resistance exercise training. Most of the studies dealing with normobaric hypoxic resistance training investigated the potential added value over normoxic resistance training on muscle mass and muscle strength, with divergent conclusions. Larger gains in muscle size (CSA, muscle mass, or lean mass) (14,37,56,61,62,70,101) and muscle strength (45,61,63,70,95,101) were found after hypoxic vs. normoxic training. Nevertheless, it should be mentioned that others found no additional effects on muscle mass (45,53,63,94,95) and strength (26,37,41,53,56,62,94). Based on those results, no consensus can be reached as to whether hypoxic conditions offer added value to the gains in muscle strength and muscle mass usually observed after resistance training. This said, as about half of the studies revealed a further increase in muscle strength or muscle mass by hypoxic training; hypoxic training might be of interest for some athletes under certain conditions.

Acute Changes in Protein Balance and Satellite Cells

Skeletal muscle mass results from the balance between protein synthesis and degradation. Satellite cell inclusion may also contribute to increased muscle mass, whereas fiber loss results in a reduction of muscle mass. At the molecular level, the number, size, and type of fibers are different features that are regulated by various signaling pathways. Although controversial (35), protein synthesis is regularly assessed by measuring the activation of the Akt/mammalian target of rapamycin (mTOR) pathway and its downstream targets ribosomal S6 kinase 1 (S6K1) and ribosomal S6 protein (S6). Muscle protein degradation is mainly regulated by the autophagy-lysosomal and ubiquitin-proteasome pathways. The latter mechanism is largely regulated by E3 ligases such as muscle atrophy F box (Mafbx) and muscle ring finger protein-1 (MuRF-1) (8). The transcriptional regulation of those E3 ligases is partly controlled by the members of the forkhead FoxO family, themselves down-regulated by Akt (91).

After a single resistance exercise session, the protein synthesis rate seems to be unchanged (68) or blunted (21,31) in normobaric hypoxia compared with normoxia. Etheridge et al. (21) showed that muscle protein synthesis was blunted by hypoxia after resistance training, although no amino acids were provided to favor muscle anabolism and the hypoxic conditions were more severe (FiO_2 12% for 3.5 h, 2.5 h recovery in hypoxia) than typically used by athletes (FiO_2 14–15% for 45–60 minutes and recovery in normoxia). As the hypoxic dose is crucial for muscle mass regulation (15), Gnimassou et al. (32) hypothesized that different doses could induce different responses and that resistance exercise performed in moderate hypoxia could induce a positive protein balance and favor muscle mass accretion when repeated. Contrary to this hypothesis, a lower dose of hypoxia blunted protein synthesis. The authors explored the molecular mechanisms that impaired protein synthesis after resistance exercise in hypoxia, although no modification of the Akt/mTOR pathway after hypoxic vs. normoxic exercise was found during the 4-h recovery in normoxia, despite lower AMPK phosphorylation and lower REDD1 expression. The Akt/mTOR pathway was not modified either by hypoxia in Etheridge et al. (21), as measured by unchanged phosphorylation of Akt, mTOR, eukaryotic initiation factor 4E (eIF4E), eIF4E-binding protein 1 (4E-BP1), and eukaryotic elongation factor 2. Only S6K1 phosphorylation was higher both at rest and during the 2.5-h recovery period in hypoxic compared with normoxic conditions, pointing out a disconnect between mTOR signaling and muscle protein synthesis, as previously shown in other circumstances (6,17). Recently, Moberg et al. (68) found that during the 3-h recovery period in normoxia, the increase in S6K1 phosphorylation induced by resistance exercise was blunted by about 50% when the session was performed in hypoxia compared with normoxia. Despite a reduced phosphorylation of S6K1, no difference in protein

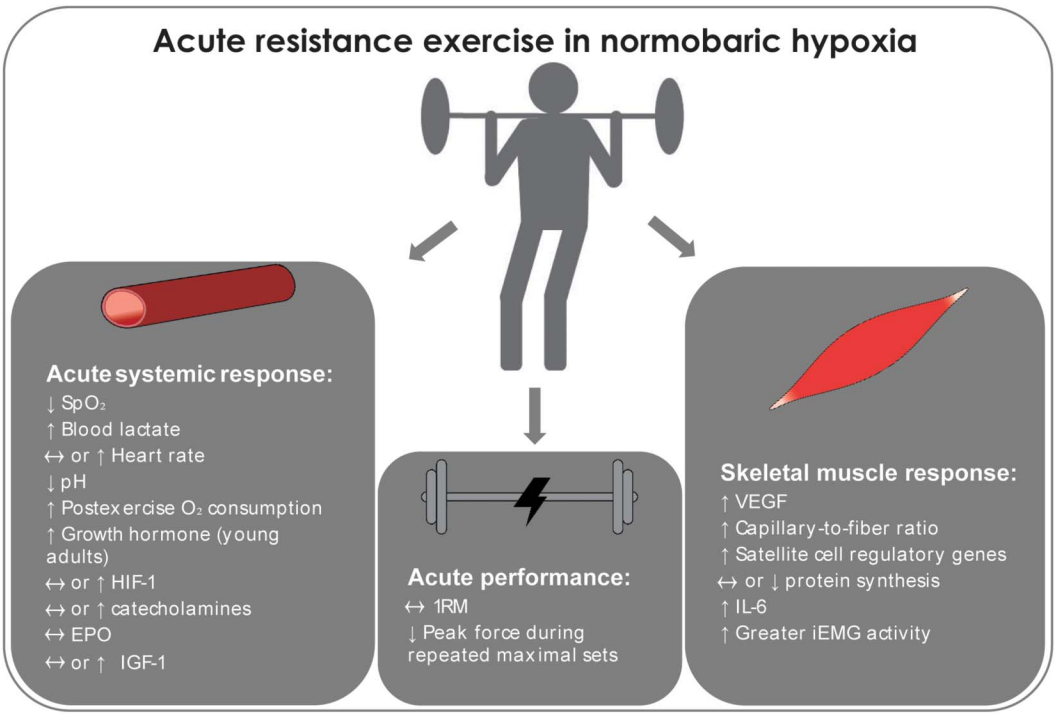

Figure 1. The effects of normobaric hypoxia on the responses to an acute resistance training session, when compared with performing resistance exercise in normoxia at the same % 1 repetition maximum (1RM). Arterial oxygen saturation (SpO_2), erythropoietin (EPO), hypoxia-inducible factor-1 (HIF-1), vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF-1), integrated electromyography (EMG).

synthesis was found 24 h postexercise in hypoxia. In conclusion, contrary to the hypothesis that hypoxic conditions could stimulate the anabolic response to resistance exercise, if anything, there is a lack of or a blunting effect on protein synthesis and the Akt/mTOR pathway. Although microRNAs may play a role in the regulation of muscle mass through pathways such as Akt/mTOR (102), there is currently no human data investigating the possible modulation of microRNAs by normobaric hypoxia in humans after resistance exercise.

Looking at the opposite side of the muscle protein balance, Gnimassou et al. (31) found that the rate of protein degradation was similar after normoxic and hypoxic resistance exercise. At a molecular level, MuRF-1 and Mafbx mRNA levels and LC3bII/I and p62 protein expression (2 markers for the autophagy-lysosomal pathway) were not modified after hypoxic compared with normoxic resistance exercise. Similar results were observed by Moberg et al. (68), who did not find differences between resistance exercise in hypoxia vs. normoxia in several markers for the ubiquitin-proteasome and the autophagy-lysosomal pathways. Although calculation of the net protein balance was not possible in Gnimassou et al. (31) because of the use of 2 different isotopes, the results suggested that the exercise session in normoxia induced a more favorable protein balance than in normobaric hypoxia. Those results contradict the idea that hypoxic conditions might favor muscle adaptations and accelerate muscle mass gains in athletes. However, a microarray analysis from the same study revealed that hypoxia regulated the expression of genes involved in myoblast differentiation/fusion and in muscle contraction machinery after hypoxic resistance training (31). Globally, genes related to the slow muscle fiber phenotype were down-regulated, such as troponin 1 and troponin T1, whereas those related to the fast phenotype were up-regulated, such as troponin T3 and MYH1, after hypoxic compared with normoxic resistance training. Those results were confirmed by qPCR acutely but not on the longer term after a whole training protocol, as mentioned below (26,95).

As mentioned earlier, satellite cells may contribute to muscle hypertrophy (103). Their activation, proliferation, and differentiation are tightly controlled by the so-called myogenic regulatory factors, namely myogenin, MyoD, myf-5, and Mrf4 (103). Gnimassou et al. (31) found higher mRNA levels of myogenin in hypoxia compared with normoxia, both at rest and after exercise. A trend for an increase in MyoD and Mrf4 mRNA levels was also observed, suggesting a potentially higher contribution of satellite cells to muscle adaptation in hypoxic vs. normoxic conditions. In a follow-up study, it was hypothesized that activation of satellite cells and subsequent myogenesis could be triggered by inflammation (9). Indeed, hypoxic resistance exercise promoted acute inflammation and macrophage activation mediated by the TNFα/NF-κB/IL-6/STAT3 pathway. Those results were corroborated in vitro in human primary myotubes, in which myogenesis was activated by hypoxia through increased mRNA levels of Myf5, MyoD, myogenin, and Mrf4 and was blunted by siRNA targeting STAT3. Based on those results, it is possible that satellite cells might have a key role in skeletal muscle adaptations induced by hypoxic resistance training. Considering the role of inflammation-induced macrophage activation in satellite cell function and muscle regeneration, it is tempting to hypothesize that hypoxia could foster muscle regeneration postexercise and thus accelerate muscle adaptation to resistance training. Whether the acute responses to hypoxic resistance exercise translate into muscle adaptations to resistance training needs to be further clarified.

Intramuscular Adaptations

Only limited data exist on the intramuscular mechanisms induced by normobaric hypoxic resistance training as only 3 studies took muscle biopsies. The first study did not reveal any difference in mRNA markers of hypoxia (VEGF and myoglobin), glycolytic enzymes (PFK), lactate dehydrogenase A/B, or myosin heavy chain isoforms between hypoxic and normoxic resistance training (26). A large interindividual variability was found, which probably contributed to the lack of effects. The second study measured markers for mitochondrial biogenesis and angiogenesis, such as PGC-1α, citrate synthase (CS) activity, nitric oxide synthase, VEGF, HIF-1, and capillary-to-fiber ratio (53). The expression or activity of those intramuscular markers for mitochondrial biogenesis and angiogenesis was not different after hypoxic vs. normoxic resistance training. However, plasma VEGF levels and capillary-to-fiber ratio were increased only after hypoxic resistance training, not after normoxic training. Those results suggest a greater angiogenesis in skeletal muscle after hypoxic vs. normoxic resistance training, which could have contributed to the larger gain in muscular endurance in hypoxia. The third and most recent study aimed at investigating the involvement of satellite cells in the response to hypoxic compared with normoxic resistance training (95). Despite greater gains in muscle strength after hypoxic vs. normoxic resistance training, only early myogenesis, as measured by higher MyoD and Myf5 mRNA levels, appeared to be enhanced by hypoxia compared with normoxia. The protein expression of myosin heavy chain isoforms SDH and CS (2 markers for oxidative metabolism) and monocarboxylate transporter 1 and 4 (lactate transporters) were not different between hypoxia and normoxia. As neither the mRNA or the protein levels nor the expression of HIF-1α target genes were different between hypoxic and normoxic conditions, it was concluded that the few molecular changes observed in that study were independent of HIF-1α. Although larger gains in muscle strength and mass and in explosivity and speed may be observed after hypoxic resistance training, the underlying molecular mechanisms remain poorly investigated and understood. More studies are needed to better understand the intramuscular mechanisms contributing to muscle adaptations to long-term hypoxic resistance training.

Physiological Responses to Resistance Training in Hypoxia

Numerous physiological responses have been characterized after resistance exercise in hypoxia, including metabolic, hormonal, and hematological parameters (Figure 1).

Relative Exercise Intensity, Exercise Performance

Relative exercise intensity may partly explain the physiological response to hypoxic resistance exercise. Theoretically, performing resistance training in hypoxic conditions requires a higher relative exercise intensity compared with performing the same resistance exercise in normoxic conditions. Although there is strong evidence that aerobic performance (e.g., V_{O_2}peak and peak power) is reduced in hypoxia (FiO_2 14.0–15.0%) compared with normoxia (57,74), the resistance training literature is less clear.

Scott et al. (85) showed that resistance exercise can be performed at 80% 1RM in hypoxia (5 × 5 repetitions; 3 minutes rest; FiO_2 13.0%) without any decrement to physical performance, perceptual ratings, or self-reported muscle soreness. Ramos-Campo et al. (78) also reported no decrement to power output of a bench press exercise when performed at 6RM to failure in normobaric hypoxia (FiO_2 13.0 and 16.0%; 3 minutes rest) compared with the same exercise in normoxia. Furthermore, no loss of power output occurred during 6 sets of 15 seconds of maximal jump exercises in hypoxia (FiO_2 16.5 and 13.5%; 3 minutes rest) compared with normoxia (5). Karayigit et al. (48) compared a maximal strength test in hypoxia and normoxia, showing that 1RM performance of a squat and bench press was not lower in hypoxia (FiO_2 12.0% or 16.0%) compared with normoxia. However, bench press endurance was decreased in hypoxia compared with normoxia, and Ramos-Campo et al. (77) also reported lower peak force and peak power when performing half squats at 60% 1RM in FIO_2 13.0% to failure compared with normoxia. Therefore, it is possible that maximal strength and explosive movements performed in small set/rep ranges are unaffected in hypoxic conditions, but that repeated bouts of high-intensity resistance exercise to failure may be impaired in hypoxic conditions. Considering that recovery between exercise sets is largely influenced by oxidative metabolism, it is not unreasonable to hypothesize that hypoxia could impair the recovery process (27). This raises an important consideration in the prescription of resistance training in hypoxia. Although it appears that training programs performed to/near failure can elicit favorable training outcomes, selecting training parameters and a hypoxic dose that are too intense could reduce exercise performance to an extent that impacts the long-term training outcomes. If very high-intensity exercises are prescribed with short interset rest periods, large set/repetitions, and a severe hypoxic dose ($<FIO_2$ 12.0%), individuals may fail to complete these sets in hypoxic conditions, thus achieving a lower total training load compared with normoxia. Not all resistance training studies in hypoxia reported the total training load completed between normoxic and hypoxic groups, although it is certainly possible to match training loads using a moderate level of hypoxia and moderate-to-high exercise intensity/set range, even in older adults (4). For example, adults aged 60–70 years were able to successfully complete 4 sets and 10 repetitions of upper- and lower-body exercises with 1-minute rest periods in FIO_2 14.4% (4). Across the 8-week training period, the total load performed by normoxic and hypoxic groups was not different.

Hypoxia also increases muscle fiber recruitment during resistance training, evidenced by greater integrated electromyography values in the *vastus lateralis* during 3 sets of 10 squats performed at 60% 1RM in hypoxia (FiO_2 16.0%; 1-minute rest) compared with normoxia (86). Some have theorized that the increased muscle fiber recruitment helps to maintain muscle force output despite increased fatigue caused by the hypoxic environment (66,93). Future research is needed to clarify the muscle fiber recruitment response to hypoxic resistance exercise and the underlying mechanisms.

Sympathetic Nervous System Activity

Although the hypoxic training literature is much more advanced for endurance exercise than resistance exercise, comparison between the 2 training modes is difficult in the context of ANS activity. The endurance training literature often matches hypoxic and normoxic training groups by relative exercise intensity because the percentage of maximal oxygen uptake (V_{O_2}max) and heart rate are typically higher in hypoxia at any given absolute training intensity compared with normoxia (36). This

methodology typically results in a lower absolute training intensity in hypoxia compared with normoxia, where individuals reach a given percentage of their V_{O_2}max at a lower running/cycling speed (i.e., wattage) when exercising in hypoxia compared with normoxia. For example, Morishima et al. (69) instructed their subjects to cycle at the equivalent of 60% V_{O_2}max in both normoxia and hypoxia. This likely means that subjects achieved 60% of their V_{O_2}max at a lower wattage in hypoxia compared with normoxia. Conversely, resistance training protocols in hypoxia are typically matched for absolute training load using % 1RM. Performing the same resistance exercise load in hypoxia, therefore, likely drives sympathetic activity to a greater extent than normoxia through multiple mechanisms.

Acute hypoxic exposure (e.g., SpO_2 77–87%) increases sympathetic activity, likely through the activation of peripheral chemoreceptors that mediate their actions through a structure in the brainstem called the rostral ventrolateral medulla (38,100). The medulla can be directly stimulated by acute hypoxia exposure, although the severity of hypoxia required for direct stimulation is likely higher than for peripheral chemoreceptors in the vasculature (92). The high degree of metabolic stress caused by performing exercise in hypoxic conditions (e.g., decreased pH) could stimulate sympathetic nervous system activity through activation of the muscle metaboreflex and peripheral chemoreceptors. Regardless of the mechanism, sympathetic outflow to the heart, renal, splenic, and skeletal muscle vascular beds is increased during hypoxic exercise. Although sympathetic activity has not been directly measured in hypoxic resistance exercise, Katayama et al. (49) showed that moderate intensity cycling in hypoxia (FiO_2 12.7%) elicits greater muscle sympathetic nerve activity than normoxia, even when controlling for relative exercise intensity. This response may partly function to facilitate vasodilation of blood vessels that supply skeletal muscle, thus compensating for the reduced O_2 supply in hypoxic conditions (a phenomenon termed "compensatory vasodilation" (46)). The findings of Horiuchi et al. (44) support this theory, where mean arterial pressure was lower after hypoxic resistance exercise compared with normoxic exercise.

A common proxy measure for sympathetic activity in the literature is heart rate. Filopoulos et al. (25) showed a greater heart rate during high-intensity resistance exercise (85% 1RM; 5 × 3 repetitions; 3 minutes rest) in FIO_2 12.0% compared with normoxia, which suggests greater sympathetic activity in hypoxia. However, this result is not consistent (86) and likely depends on factors such as the hypoxic dose, exercise intensity, and interset rest periods. Álvarez-Herms et al. (5) measured heart rate variability (HRV) as an indicator of sympathetic activity and showed no difference between performing 6 sets of maximal effort jumps in hypoxia (FiO_2 13.5 or 16.5%; 3 minutes rest) and normoxia. It would be interesting to investigate if a shorter interset rest period elicits a greater increase in HRV compared with the relatively long 3-minute rest used by Álvarez-Herms et al. (5). A shorter interset rest period in hypoxia would likely limit recovery between sets and increase the reliance on aerobic metabolism in subsequent sets. Greater metabolic stress in hypoxia may increase muscle fiber recruitment (86) and activate the sympathetic nervous system to a greater extent than normoxia. It will be important to include more athletic populations in future research to determine the physiological load of performing resistance training in hypoxia during heavy training periods. Given the focus of autonomic fatigue in overtraining syndrome (76), careful load monitoring could be important when using hypoxic resistance training during peak training periods. Future research is needed to explore the sympathetic response to hypoxic resistance exercise and the downstream impacts on factors such as muscle blood flow and cardiovascular function.

Exercise Metabolism

Although individuals can produce relatively high intensities of resistance exercise in hypoxia, the contribution of energy systems to adenosine triphosphate (ATP) production are likely different from normoxia. Exposure to a hypoxic environment reduces SpO_2 and, therefore, can reduce the oxygen available to tissues. Although increased ventilation and heart rate can partly compensate for the reduced SpO_2 during hypoxic exposure (12), hypoxemia can temporarily reduce oxygen delivery to the muscle, particularly when hypoxia is combined with high-intensity exercise (89). There is, therefore, less oxygen supply to the mitochondria that produce ATP through oxidative phosphorylation of glucose (i.e., aerobic glycolysis) and beta oxidation of fatty acids.

Metabolic stress occurs when the demand for ATP exceeds the ability of the mitochondria to produce ATP through oxidative phosphorylation (i.e., aerobic metabolism). The decreased oxygen availability during hypoxic exercise likely increases the reliance on anaerobic ATP production from phosphocreatine (PCr) and anaerobic glycolysis (the breakdown of glucose without oxygen) (43,64). Anaerobic glycolysis provides a rapid source of ATP for high-intensity exercise independent of oxygen, although a high intensity of exercise cannot be maintained because of the accumulation of metabolic products such as hydrogen ions (H^+), inorganic phosphate (P_i), and adenosine monophosphate that cause metabolic stress (reviewed by (96)).

Blood lactate is often used as an indirect measure of anaerobic metabolism and metabolic stress. When ATP demand exceeds the production capacity of the mitochondria during intense exercise, some of the pyruvate produced by glycolysis is instead converted into lactate, which accumulates if it cannot be quickly cleared by the cell (30). Excess lactate is released into the blood where it accumulates if it cannot be cleared by other tissues such as a less active muscle (30). Performing resistance exercise (70–85% 1RM) in hypoxic conditions (FiO_2 12–14.4%; 5x3-10 repetitions; 1–3 minutes rest) typically results higher blood lactate in the 30 minutes postexercise compared with the same training in normoxia (25,51). Other studies found no effect of hypoxia on blood lactate after resistance exercise (26,56); however, this may be attributable to the low intensity of training (6 sets of 25 repetitions at 30% 1RM, 3 sets of repetitions to failure at 10RM, respectively). Nonetheless, Yan et al. (101) used a relatively high exercise intensity (5 × 10 repetitions at 70% 1RM), short interset rest periods (1 minute), and a strong hypoxic dose (FIO_2 12.6%) and found no differences in blood lactate after hypoxic and normoxic resistance exercise. The blood lactate response to resistance exercise in hypoxia appears modest compared with normoxia, and studies with small sample sizes may be unable to detect the differential response between conditions.

A more direct measure of metabolic stress is to measure pH after hypoxic exercise. Excess H^+ produced in the muscle during exercise is transported into the bloodstream and subsequently reduces the pH of the blood. Metabolic acidosis occurs when the rate of H^+ production exceeds the ability of the cell to remove H^+ through buffers such as bicarbonate (HCO_3^-), amino acids, and proteins (80). Ramos-Campo et al. (77) showed that venous HCO_3^- and pH were significantly lower after resistance exercise performed 3 sets at 100% 6RM in FiO_2 13.0% (1-minute

rest) compared with normoxia, suggesting that hypoxia caused a greater level of metabolic stress than normoxia. The hypoxic environment likely caused a greater accumulation of H^+ (and thus a lower pH) because the rate of mitochondrial respiration failed to match the high rate of glycolysis and ATP hydrolysis in the low oxygen environment. The authors also included a group that trained in FIO_2 16.0%, who did not show significant changes in venous HCO_3^-, pH, or lactate compared with normoxia, suggesting that a more severe hypoxic dose is required to disturb acid-base homeostasis with resistance training.

From a performance perspective, the metabolic stress induced by completing resistance exercise in moderate hypoxia may contribute to a decreased exercise capacity during maximal, repeated sets of resistance exercise. This theory is supported by the literature, where maximal strength is unaffected by hypoxic conditions (1RM strength test in FiO_2 14 or 16%) (48) but peak power is reduced during repeated sets of intense resistance exercise in hypoxia compared with normoxia (3 sets of half squats with 3 minutes rest) (77). Ultimately, prescribing high set ranges, short interset rest periods, and a lower FiO_2% is likely to cause the greatest level of metabolic stress during resistance exercise in hypoxia. Although there is currently no mechanistic link, the greater metabolic stress of hypoxic resistance exercise may enhance muscular endurance performance to a greater extent than the same training in normoxia (53). Exercise professionals should consider the nature of their sport when prescribing hypoxic resistance exercise, considering whether their aim is to increase muscular endurance or maximal strength. If coaches are targeting increases in maximal strength, moderate hypoxic doses (approx. FIO_2 14%) and moderate interest rest periods (1 minute) may be more ideal to avoid large decreases in maximal force output that could occur in severe hypoxic conditions with short interset rest periods.

The mechanisms causing the reduced force output during repeated sets of intense resistance exercise in hypoxia are not entirely clear, although could be mediated at the skeletal muscle level (peripheral fatigue) or at the central nervous system level (central fatigue, where changes in neural drive can impact muscle performance (96)). One factor that is uncharacterized in the literature is the rate of PCr resynthesis during repeated sets of resistance training in hypoxia. Ramos-Campo et al. (78) showed that oxygen consumption was 28% higher in the 20 minutes after hypoxic resistance exercise compared with normoxic exercise (3 sets of upper-/lower-body exercises at 100% 6RM, 3 minutes rest). The authors suggested that the greater postexercise oxygen debt may have been partly caused by a greater requirement for PCr resynthesis in hypoxia compared with normoxia. The hypoxic studies that used short interset rest periods likely reduced the degree of PCr resynthesis, given that short rest periods provide only a small opportunity to restore PCr stores that support ATP production during intense exercise. High-intensity interval training (HIT) protocols in hypoxia can improve PCr kinetics (42), and it would, therefore, be interesting to examine if resistance training in hypoxia can improve PCr kinetics.

Exercise Metabolism: Metabolic Disease

The combination of exercise and hypoxia present an interesting strategy to improve insulin sensitivity and glucose tolerance in individuals with obesity and type II diabetes. Resistance exercise drives muscle hypertrophy and typically increases glucose tolerance through increased insulin sensitivity (22) and greater glycogen synthesis (73). Hypoxia may increase the magnitude of muscle hypertrophy in response to resistance exercise (70); therefore, hypoxia could also increase the effect of resistance training on insulin sensitivity and glucose tolerance. Although the effect of hypoxic resistance training on metabolic disease has never been studied, 2 studies characterized the glucose response to hypoxic resistance training in healthy adults. No effect of resistance training (3 sets of upper-/lower-body exercises at 6RM; 3 minutes rest), whether in normoxia or in hypoxia, was observed on basal blood glucose, plasma triglycerides, total cholesterol, high-density lipoprotein, or low-density lipoprotein levels in healthy young adults (62). Fasting blood glucose and total cholesterol were also unaffected by 8 weeks of resistance training in FIO_2 14.4% (4 × 10 repetitions; 1-minute rest) in older adults (4). The only study to measure insulin responses to resistance training in hypoxia found no changes to insulin, homeostatic model assessment for insulin resistance, or blood glucose in the 60 minutes postexercise in healthy older adults (3). After 8 weeks of training, there were still no changes to fasting or postexercise insulin levels, although these individuals had a BMI <25 and were free from metabolic disease. Future research is needed to determine the metabolic responses to hypoxic resistance training in populations with metabolic dysfunction. Research is also needed into glucose kinetics and insulin action during hypoxic resistance exercise.

We can draw from the endurance training literature to understand the potential benefits of hypoxic exercise in metabolic disease. Endurance exercise performed in hypoxia (FiO_2 14.6%; 60 minutes at 90% lactate threshold) increased insulin sensitivity in type II diabetic patients to a greater extent than normoxia (59). Hypoxia (FiO_2 14.7%) increased the glucose uptake response to endurance exercise (60 minutes of continuous exercise at 90% lactate threshold) in diabetic patients when compared with normoxia (60). Moreover, 6 weeks of mixed training (endurance and resistance exercise; 50–60 minutes of intermittent cycling at 50–80% MAP and 4 × 6 repetitions of upper-/lower-body exercises performed at 70% 1RM) performed in hypoxia increased glucose utilization during exercise in comparison with normoxia in obese adolescents, which is beneficial for glucose tolerance (18). To date, there are no studies showing detrimental metabolic responses to hypoxic resistance exercise, nor any studies that thoroughly characterize the glucose flux and insulin responses using thorough techniques such as isotope labelling.

Exercise Metabolism: Fuel Utilization and Nutrient Status

There is currently very little focus on fuel utilization or the impact of nutrient status during resistance exercise in hypoxia. Theoretically, there is greater reliance on carbohydrate metabolism to anaerobically produce ATP in a hypoxic environment (43,64). Although resistance training protocols are relatively short in duration and unlikely to significantly deplete glycogen stores, future research may investigate the role of nutrient status (carbohydrate, protein, and fat consumption) on the metabolic responses to resistance training. If athletes are performing multiple sessions of hypoxic resistance training or performing this training method after aerobic exercise or fasting, they should consider if their glycogen status and carbohydrate availability might impair their ability to anaerobically produce ATP during hypoxic resistance training. Training in a glycogen depleted state could theoretically reduce the ability of an individual to perform repeated sets of high-intensity resistance exercise in hypoxia.

Hormonal and Hematological Factors

Among the most studied hormonal adaptations, growth hormone and insulin-like growth factor (IGF-1) levels have repeatedly been measured at rest, during, and after resistance training in hypoxia. This is not surprising because of their putative role in muscle hypertrophy, although the role of growth hormone has been questioned regularly (28).

Growth Hormone

Human growth hormone (somatotropin) typically increases in the 60 minutes after resistance exercise (55), where it promotes tissue metabolism and repair (19). Several studies showed that hypoxia further increases the magnitude of growth hormone release in venous blood up to 30 minutes after an acute bout of resistance exercise (25,51,52,56,101). Three studies have also showed that the higher circulating growth hormone levels after hypoxic resistance exercise persist after 5–8 weeks of training (53,56,101). Some studies suggested that the elevated growth hormone response may underpin the superior muscle hypertrophy and strength adaptations seen in hypoxic training (56,101). However, Kon et al. (52) found a significant increase in growth hormone after hypoxic exercise (5 × 14 repetitions of bench press/leg press at 50% 1RM; 1-minute rest) but not normoxic exercise, though found a similar increase in muscle CSA in normoxic and hypoxic conditions. Therefore, the greater growth hormone release in hypoxia was not systematically related to greater muscle hypertrophy (53). It appears that growth hormone was not related to muscle hypertrophy after hypoxic training as previously observed in other conditions (28).

There is more solid evidence that growth hormone administration stimulates protein synthesis in soft tissues, potentially reducing the risk of ligament damage and strengthening skeletal muscle tendon attachments (19). To our knowledge, no one has investigated tendon and ligament stiffness or elasticity after hypoxic resistance training. Growth hormone is also widely recognized for its important role in metabolism, where it promotes lipolysis in times of fasting and stress (71). These metabolic properties of growth hormone are important for the maintenance of body composition and nutrient homeostasis. Although the long-term effectiveness of regular hypoxic resistance training for weight management is unclear, Park et al. (72) observed a larger reduction in fat mass in obese older males after 12 weeks of hypoxic training (60 minutes treadmill/bicycle at 60–70% heart rate maximum and 3 × 10 repetitions of resistance band exercises) compared with normoxic training. In contrast, De Groote et al. (18) showed that mixed aerobic (intermittent cycling at 50–80% MAP) and resistance training (4 × 6 repetitions of lower-/upper-body exercises at 70% 1RM; 2 minutes rest) performed in hypoxia has no additive effects on fat mass depletion in comparison with normoxic training in adolescents with obesity. Currently, there are no long-term studies investigating the metabolic responses to hypoxic training, nor is there any knowledge of the long-term hormonal responses to this training strategy beyond 8 weeks.

Currently, little is known about the mechanisms mediating the greater growth hormone response with hypoxia. Growth hormone is regulated by the release of growth hormone releasing hormone (GHRH) from the anterior pituitary and is stimulated by factors such as nutrient status, stress, and intense exercise (reviewed by (50)). Exercise-induced growth hormone release is likely intensity dependent and is linked with the onset of lactate threshold (32,33) and the accumulation of metabolic subproducts such as H^+ during exercise (34). In vitro studies suggest that catecholamines stimulate growth hormone secretion from the pituitary through sympathetic pathways (29). Therefore, the greater metabolic stress and activation of sympathetic pathways might contribute to the greater growth hormone response to hypoxic resistance exercise, although neither Kurobe et al. (56) (3x elbow extensions performed at 10RM to failure in 12.7%; 1-minute rest) nor in Yan et al. (101) (5 × 10 repetitions of back squat at 70% 1RM in FiO_2 16% or 12.6%; 1-minute rest) found changes in blood lactate levels to explain the elevated growth hormone in hypoxia. Therefore, growth hormone regulation in hypoxia and the role of growth hormone during and after hypoxic resistance training remains unclear. Future research could focus on the release of factors that regulate GHRH release from the pituitary, such as leptin, which is responsive to hypoxia (90) and influences GHRH release from the pituitary (97).

Contrary to young adults, older adults do not experience an increase in systemic growth hormone after 4 × 10 sets of 70% 1RM resistance exercise in 14.4% O_2 compared with normoxia (3). Surprisingly, the older adults in this study showed a blunted growth hormone response to resistance exercise after an 8-week resistance training program in hypoxia compared with normoxia. The causes and potential consequences of this response remain unclear. Hypoxic resistance exercise certainly does not appear to be an effective strategy to combat the age-related decline in growth hormone.

IGF-1

IGF-1 is frequently reported in the literature because of its potential role in muscle hypertrophy. IGF-1 is primarily released from the liver upon stimulation by growth hormone, although it is also produced by peripheral tissues including skeletal muscle where it promotes protein synthesis and inhibits protein degradation (reviewed by (81)). Two studies compared the resting levels of IGF-1 after hypoxic and normoxic resistance training. Chycki et al. (14) found higher resting IGF-1 levels after performing resistance training (8 sets of 10 repetitions at 70% 1RM, 3 minutes rest) for 6 weeks in hypoxia (FIO_2 12.9%) compared with normoxic training. Conversely, Kon et al. (53) found that resting IGF-1 levels were not different after 8 weeks of resistance training (5 sets of 10 repetitions at 70% 1RM, 1.5 minutes rest) in hypoxia (FIO_2 14.4%) compared with normoxia. In addition, Kon et al. (53) found no differences in resting circulating testosterone, cortisol, IGF-binding protein-3, red blood cells, hemoglobin, or hematocrit between normoxic and hypoxic resistance training. Interestingly, a higher fat-free mass was found in hypoxic conditions in the first (14) but not in the second study (53), suggesting that IGF-1 could be an essential factor in the hypertrophic response to hypoxic resistance training. It is possible that the higher set ranges and greater hypoxic dose contributed to the greater responses observed by Chycki et al. (14).

Cortisol

Cortisol typically increases during exercise through sympathetic stimulation, likely up-regulating lipolysis, protein degradation and gluconeogenesis to meet the metabolic demands of exercise (10,54). Although hypoxia might increase the sympathetic response to resistance exercise, hypoxia does not appear to further increase cortisol in the 60 minutes after resistance exercise (14,40,51–53,56,101). Yan et al. (101) showed that 5 weeks of high-intensity resistance training (5 × 10 repetitions of a back squat at 70% 1RM; 1-minute

rest) in FiO_2 12.6% significantly reduced resting and postexercise cortisol levels in young healthy male athletes. However, older adults do not show changes to resting or postexercise cortisol levels after 8 weeks of hypoxic (FiO_2 14.4%; 4 × 10 repetitions of upper-/lower-body exercises at 70% 1RM; 1-minute rest) resistance training (3). Although no differences in testosterone have been reported after hypoxic resistance exercise in young (101) or older adults (3), Yan et al. (101) also reported a greater cortisol/testosterone ratio after the last session of the 5-week hypoxic resistance training program. Authors explained that the result was because of significantly lower cortisol levels in the hypoxic group and theorized that this may represent a more favorable anabolic environment for muscle hypertrophy. Ultimately, it appears that the testosterone and cortisol responses to resistance training are not substantially different to traditional normoxic training.

Norepinephrine and Epinephrine

Kon et al. (51) showed that norepinephrine and epinephrine were significantly elevated in the 60 minutes after moderate intensity hypoxic resistance exercise (FiO_2 13.0%; 5 × 10 repetitions of bench press/leg press at 70% 1RM; 1-minute rest) compared with normoxic exercise. Norepinephrine concentrations alter carbohydrate utilization during exercise by increasing skeletal muscle glycogenolysis and pyruvate dehydrogenase activation (98). Although catecholamines are not direct measures of sympathetic nervous activity, the sympathetic nervous system may mediate some of the metabolic responses to resistance exercise in hypoxia through catecholamine secretion, although no firm link has been established.

Other Hematological Factors

Plasma hemoglobin, erythropoietin, and hematocrit appear to be unresponsive to resistance training, whether in normoxia or in hypoxia (4,37,94). The unchanged hemoglobin and hematocrit seem logical after hypoxic resistance training considering the short exposure to hypoxia compared with endurance athletes who usually increase those parameters using chronic stays at altitude (67). An increase in the frequency, duration, and severity of hypoxia is likely needed to elicit such improvements in red blood cell mass and associated measures.

Although hypoxia is a known regulator of inflammatory and immune pathways (16), little is known about the effects of combined resistance training and hypoxia on these factors. This is surprising given that the immune health and inflammatory status of athletes is crucial for their participation throughout competitions seasons. In young adults, acute resistance exercise in hypoxia (FiO_2 14.4%; 4 × 10 repetitions at 70% 1RM; 1-minute rest) increases the number of circulating neutrophils in the hours after exercise compared with normoxia (2). The amplified neutrophil response may be beneficial for responding to pathogens and the repair of damaged skeletal muscle after exercise, although further investigation is needed. Importantly, it appears that performing hypoxic resistance training does not negatively impact postexercise immunity, with the other 4 major white blood cell populations unaffected by the addition of hypoxia to training. In older adults, hypoxia increases the lymphocyte response to resistance exercise (FiO_2 14.4%; 4 × 10 repetitions at 70% 1RM; 1-minute rest) to a greater extent than normoxia, which may be beneficial for immune function (1). Although hypoxia does not alter the systemic inflammatory cytokine response to acute resistance training in older adults (1), young adults show a greater increase in plasma interleukin-6 (IL-6) and IFNg after hypoxic resistance exercise (FiO_2 14%; 8 × 8 repetitions of knee extension at 80% 1RM; 2 minutes rest), suggesting that hypoxia augments the inflammatory response to exercise (9).

The use of hypoxic resistance training is a growing strategy that aims to enhance hypertrophy and strength adaptations. There is currently no consensus on the overall effectiveness of hypoxic resistance training for strength and hypertrophy adaptations, nor the underlying biochemical pathways involved. However, there are interesting physiological responses that are amplified by performing resistance training in hypoxia. These include likely changes to energy system contribution during hypoxic exercise and amplified metabolic stress, hormone release and cytokine production, sympathetic nervous system activity, and other hypoxia-induced cellular pathways. There are currently many gaps in our understanding of the physiological responses to hypoxic resistance training, partly caused by the infancy of the research field and diversity of hypoxic and training parameters.

Practical Applications

Performing resistance exercise in normobaric hypoxia elicits greater hormonal, metabolic, and skeletal muscle responses compared with normoxia. Targeting a large metabolic stress response to hypoxic resistance exercise may elicit the largest training adaptations, although the exact mechanisms underpinning these training adaptations are not yet clear. Sporting coaches and sport scientists should carefully select hypoxic training parameters; selecting a mild hypoxic dose, low set/rep range, and long interset rest period will likely fail to elicit superior training adaptations over traditional normoxic exercise. Conversely, selecting a more severe hypoxic dose, a high exercise intensity and short interset rest periods may hinder the ability of athletes to reach their 1RM and may blunt the rate of protein synthesis in their skeletal muscle. Training parameters that induce high levels of metabolic stress include a moderate hypoxic dose (FIO_2 ≤15%), short interset rest period (1 minute), moderate-high exercise intensity (≥70% 1RM), and moderate-large set/rep range (≥3 sets of ≥10 repetitions, ideally performed to failure, or close to failure). The future inclusion of athletic populations in the training literature will help determine the potential benefits of hypoxic training; few studies have included elite athletes during competition season to determine how trained individuals may respond both acutely and chronically. Training load and nutrient status may also be important considerations for athletic populations to optimize the adaptations to hypoxic training.

Acknowledgments

The authors have no conflicts of interest to disclose. G. L. Allsopp, F. A. Britto, C. R. Wright, and L. Deldicque contributed to the drafting of the manuscript. All authors gave final approval of the manuscript publication and take accountability for all aspects of the work.

References

1. Allsopp G, Addinsall A, Stephenson G, et al. The acute leukocyte and cytokine response of older adults to resistance exercise in normobaric hypoxia. *Biol Sport* 40: 425–438, 2023.

2. Allsopp G, Barnard J, Goodear S, et al. The effects of normobaric hypoxia on the leukocyte responses to resistance exercise. *Biol Sport* 40: 101–109, 2023.
3. Allsopp GL, Addinsall AB, Hoffmann SM, Russell AP, Wright CR. Hormonal and metabolic responses of older adults to resistance training in normobaric hypoxia. *Eur J Appl Physiol* 122: 1007–1017, 2022.
4. Allsopp GL, Hoffmann SM, Feros SA, Pasco JA, Russell AP, Wright CR. The effect of normobaric hypoxia on resistance training adaptations in older adults. *J Strength Cond Res* 36: 2306–2312, 2022.
5. Álvarez-Herms JJ-s, Julià-Sánchez S, Gatterer H, Corbi F, Viscor G, Burtscher M. Effects of a single power strength training session on heart rate variability when performed at different simulated altitudes. *High Alt Med Biol* 21: 292–296, 2020.
6. Atherton PJ, Etheridge T, Watt PW, et al. Muscle full effect after oral protein: Time-dependent concordance and discordance between human muscle protein synthesis and mtorc1 signaling. *Am J Clin Nutr* 92: 1080–1088, 2010.
7. Berra E, Roux D, Richard DE, Pouysségur J. Hypoxia-inducible factor-1 alpha (hif-1 alpha) escapes o(2)-driven proteasomal degradation irrespective of its subcellular localization: Nucleus or cytoplasm. *EMBO Rep* 2: 615–620, 2001.
8. Bodine SC, Latres E, Baumhueter S, et al. Identification of ubiquitin ligases required for skeletal muscle atrophy. *Science* 294: 1704–1708, 2001.
9. Britto FA, Gnimassou O, De Groote E, et al. Acute environmental hypoxia potentiates satellite cell-dependent myogenesis in response to resistance exercise through the inflammation pathway in human. *FASEB J* 34: 1885–1900, 2020.
10. Budde H, Machado S, Ribeiro P, Wegner M. The cortisol response to exercise in young adults. *Front Behav Neurosci* 9: 13, 2015.
11. Burtscher M, Pachinger O, Ehrenbourg I, et al. Intermittent hypoxia increases exercise tolerance in elderly men with and without coronary artery disease. *Int J Cardiol* 96: 247–254, 2004.
12. Camacho-Cardenosa A, Camacho-Cardenosa M, Tomas-Carus P, Timón R, Olcina G, Burtscher M. Acute physiological response to a normobaric hypoxic exposure: Sex differences. *Int J Biometeorol* 66: 1495–1504, 2022.
13. Chen S, Murphy J, Toth R, Campbell DG, Morrice NA, Mackintosh C. Complementary regulation of tbc1d1 and as160 by growth factors, insulin and ampk activators. *Biochem J* 409: 449–459, 2008.
14. Chycki J, Czuba M, Gołaś A, et al. Neuroendocrine responses and body composition changes following resistance training under normobaric hypoxia. *J Hum Kinet* 53: 91–98, 2016.
15. D'Hulst G, Deldicque L. Human skeletal muscle wasting in hypoxia: A matter of hypoxic dose? *J Appl Physiol* 122: 406–408, 2017.
16. D'Ignazio L, Bandarra D, Rocha S. Nf-κb and hif crosstalk in immune responses. *FEBS J* 283: 413–424, 2016.
17. de Boer MD, Selby A, Atherton P, et al. The temporal responses of protein synthesis, gene expression and cell signalling in human quadriceps muscle and patellar tendon to disuse. *J Physiol* 585: 241–251, 2007.
18. De Groote E, Britto FA, Bullock L, et al. Hypoxic training improves normoxic glucose tolerance in adolescents with obesity. *Med Sci Sports Exerc* 50: 2200–2208, 2018.
19. Doessing S, Heinemeier KM, Holm L, et al. Growth hormone stimulates the collagen synthesis in human tendon and skeletal muscle without affecting myofibrillar protein synthesis. *J Physiol* 588: 341–351, 2010.
20. Dzhalilova D, Makarova O. Differences in tolerance to hypoxia: Physiological, biochemical, and molecular-biological characteristics. *Biomedicines* 8: 428, 2020.
21. Etheridge T, Atherton PJ, Wilkinson D, et al. Effects of hypoxia on muscle protein synthesis and anabolic signaling at rest and in response to acute resistance exercise. *Am Journal Physiol Endocrinol Metab* 301: E697–E702, 2011.
22. Evans WJ. Effects of exercise on body composition and functional capacity of the elderly. *Gerontol A Biol Sci Med Sci* 50: 147–150, 1995.
23. Favier F, Britto F, Freyssenet D, Bigard X, Benoit H. Hif-1-driven skeletal muscle adaptations to chronic hypoxia: Molecular insights into muscle physiology. *Cell Mol Life Sci* 72: 4681–4696, 2015.
24. Feriche B, Garcia-Ramos A, Morales-Artacho AJ, Padial P. Resistance training using different hypoxic training strategies: A basis for hypertrophy and muscle power development. *Sports Med Open* 3: 12, 2017.
25. Filopoulos D, Cormack SJ, Whyte DG. Normobaric hypoxia increases the growth hormone response to maximal resistance exercise in trained men. *Eur J Sport Sci* 17: 821–829, 2017.
26. Friedmann B, Kinscherf R, Borisch S, Richter G, Bärtsch P, Billeter R. Effects of low-resistance/high-repetition strength training in hypoxia on muscle structure and gene expression. *Pflügers Archiv* 446: 742–751, 2003.
27. Gaesser GA, Brooks GA. Metabolic bases of excess post-exercise oxygen consumption: A review. *Med Sci Sports Exerc* 16: 29–43, 1984.
28. Gharahdaghi N, Phillips BE, Szewczyk NJ, Smith K, Wilkinson DJ, Atherton PJ. Links between testosterone, oestrogen, and the growth hormone/insulin-like growth factor axis and resistance exercise muscle adaptations. *Front Physiol* 11: 621226, 2020.
29. Giustina AVeldhuisJD, Veldhuis JD. Pathophysiology of the neuroregulation of growth hormone secretion in experimental animals and the human. *Endocr Rev* 19: 717–797, 1998.
30. Gladden LB. Lactate metabolism: A new paradigm for the third millennium. *J Physiol* 558: 5–30, 2004.
31. Gnimassou O, Fernández-Verdejo R, Brook M, et al. Environmental hypoxia favors myoblast differentiation and fast phenotype but blunts activation of protein synthesis after resistance exercise in human skeletal muscle. *FASEB* fj: 201800049RR, 2018.
32. Godfrey RJ, Madgwick Z, Whyte GP. The exercise-induced growth hormone response in athletes. *Sports Med* 33: 599–613, 2003.
33. Godfrey RJ, Whyte GP, Buckley J, Quinlivan R. The role of lactate in the exercise-induced human growth hormone response: Evidence from mcardle disease. *Br J Sports Med* 43: 521–525, 2009.
34. Gordon SE, Kraemer WJ, Vos NH, Lynch JM, Knuttgen HG. Effect of acid-base balance on the growth hormone response to acute high-intensity cycle exercise. *J Appl Physiol* 76: 821–829, 1994.
35. Greenhaff PL, Karagounis LG, Peirce N, et al. Disassociation between the effects of amino acids and insulin on signaling, ubiquitin ligases, and protein turnover in human muscle. *Am J Physiol Endocrinol Metab* 295: E595–E604, 2008.
36. Griffiths A, Shannon O, Matu J, King R, Deighton K, O'Hara JP. Response: Commentary on the effects of hypoxia on energy substrate use during exercise. *Sports Nutr Rev J* 16: 61, 2019.
37. Guardado IM, Ureña BS, Cardenosa AC, Cardenosa MC, Camacho GO, Andrada RT. Effects of strength training under hypoxic conditions on muscle performance, body composition and haematological variables. *Biol Sport* 37: 121–129, 2020.
38. Guyenet PG. Neural structures that mediate sympathoexcitation during hypoxia. *Respir Physiol* 121: 147–162, 2000.
39. Hayashi T, Hirshman MF, Fujii N, Habinowski SA, Witters LA, Goodyear LJ. Metabolic stress and altered glucose transport: Activation of amp-activated protein kinase as a unifying coupling mechanism. *Diabetes* 49: 527–531, 2000.
40. Ho J-Y, Huang T-Y, Chien Y-C, Chen Y-C, Liu S-Y. Effects of acute exposure to mild simulated hypoxia on hormonal responses to low-intensity resistance exercise in untrained men. *Res Sports Med* 22: 240–252, 2014.
41. Ho J-Y, Kuo T-Y, Liu K-L, Dong X-Y, Tung K. Combining normobaric hypoxia with short-term resistance training has no additive beneficial effect on muscular performance and body composition. *J Strength Cond Res* 28: 935–941, 2014.
42. Holliss BA, Fulford J, Vanhatalo A, Pedlar CR, Jones AM. Influence of intermittent hypoxic training on muscle energetics and exercise tolerance. *J Appl Physiol* 114: 611–619, 2013.
43. Hong S-S, Lee H, Kim K-W. HIF-1alpha: A valid therapeutic target for tumor therapy. *Cancer Res Treat* 36: 343–353, 2004.
44. Horiuchi M, Ni-I-Nou A, Miyazaki M, Ando D, Koyama K. Impact of resistance exercise under hypoxia on postexercise hemodynamics in healthy young males. *Int J Hypertens* 2018: 1456972, 2018.
45. Inness MW, Billaut F, Walker EJ, Petersen AC, Sweeting AJ, Aughey RJ. Heavy resistance training in hypoxia enhances 1rm squat performance. *Front Physiol* 7: 502, 2016.
46. Joyner MJ, Casey DP. Muscle blood flow, hypoxia, and hypoperfusion. *J Appl Physiol* 116: 852–857, 2014.
47. Kalfalah F, Sobek S, Bornholz B, et al. Inadequate mito-biogenesis in primary dermal fibroblasts from old humans is associated with impairment of pgc1a-independent stimulation. *Exp Gerontol* 56: 59–68, 2014.
48. Karayigit R, Eser MC, Sahin FN, et al. The acute effects of normobaric hypoxia on strength, muscular endurance and cognitive function: Influence of dose and sex. *Biology* 11: 309, 2022.
49. Katayama K, Ishida K, Iwamoto E, Iemitsu M, Koike T, Saito M. Hypoxia augments muscle sympathetic neural response to leg cycling. *Am J Physiol Regul Integr Comp Physiol* 301: R456–R464, 2011.
50. Kato Y, Murakami Y, Sohmiya M, Nishiki M. Regulation of human growth hormone secretion and its disorders. *Intern Med* 41: 7–13, 2002.
51. Kon M, Ikeda T, Homma T, Akimoto T, Suzuki Y, Kawahara T. Effects of acute hypoxia on metabolic and hormonal responses to resistance exercise. *Med Sci Sports Exerc* 42: 1279–1285, 2010.
52. Kon M, Ikeda T, Homma T, Suzuki Y. Effects of low-intensity resistance exercise under acute systemic hypoxia on hormonal responses. *J Strength Cond Res* 26: 611–617, 2012.

53. Kon M, Ohiwa N, Honda A, et al. Effects of systemic hypoxia on human muscular adaptations to resistance exercise training. *Physiol Reports* 2: e12033, 2014.
54. Kraemer WJ, Häkkinen K, Newton RU, et al. Acute hormonal responses to heavy resistance exercise in younger and older men. *Eur J Appl Physiol Occup Physiol* 77: 206–211, 1998.
55. Kraemer WJ, Ratamess NA. Hormonal responses and adaptations to resistance exercise and training. *Sports Med* 35: 339–361, 2005.
56. Kurobe K, Huang Z, Nishiwaki M, Yamamoto M, Kanehisa H, Ogita F. Effects of resistance training under hypoxic conditions on muscle hypertrophy and strength. *Clin Physiol Funct Imaging* 35: 197–202, 2015.
57. Lawler J, Powers SK, Thompson D. Linear relationship between vo2max and vo2max decrement during exposure to acute hypoxia. *J Appl Physiol* 64: 1486–1492, 1988.
58. Liu W, Shen S-M, Zhao X-Y, Chen G-Q. Targeted genes and interacting proteins of hypoxia inducible factor-1. *Int J Biochem Mol Biol* 3: 165–178, 2012.
59. Mackenzie R, Maxwell N, Castle P, Brickley G, Watt P. Acute hypoxia and exercise improve insulin sensitivity (si2*) in individuals with type 2 diabetes. *Diabetes Metab Res Rev* 27: 94–101, 2011.
60. Mackenzie R, Maxwell N, Castle P, Elliott B, Brickley G, Watt P. Intermittent exercise with and without hypoxia improves insulin sensitivity in individuals with type 2 diabetes. *J Clinical Endocrinol Metab* 97: E546–E555, 2012.
61. Manimmanakorn A, Hamlin MJ, Ross JJ, Taylor R, Manimmanakorn N. Effects of low-load resistance training combined with blood flow restriction or hypoxia on muscle function and performance in netball athletes. *J Sci Med Sport* 16: 337–342, 2013.
62. Martínez-Guardado I, Ramos-Campo DJ, Olcina GJ, et al. Effects of high-intensity resistance circuit-based training in hypoxia on body composition and strength performance. *Eur J Sport Sci* 19: 941–951, 2019.
63. Mayo B, Miles C, Sims S, Driller M. The effect of resistance training in a hypoxic chamber on physical performance in elite rugby athletes. *High Alt Med Biol* 19: 28–34, 2018.
64. McLellan TM, Kavanagh MF, Jacobs I. The effect of hypoxia on performance during 30 s or 45 s of supramaximal exercise. *Eur J Appl Physiol Occup Physiol* 60: 155–161, 1990.
65. Michiels C. Physiological and pathological responses to hypoxia. *Am J Pathol* 164: 1875–1882, 2004.
66. Miller K, Garland S, Ivanova T, Ohtsuki T. Motor-unit behavior in humans during fatiguing arm movements. *J Neurophysiol* 75: 1629–1636, 1996.
67. Millet GP, Roels B, Schmitt L, Woorons X, Richalet JP. Combining hypoxic methods for peak performance. *Sports Med* 40: 1–25, 2010.
68. Moberg M, Apró W, Horwath O, van Hall G, Blackwood SJ, Katz A. Acute normobaric hypoxia blunts contraction-mediated mtorc1- and jnk-signaling in human skeletal muscle. *Acta Physiol* 234: e13771, 2022.
69. Morishima T, Mori A, Sasaki H, Goto K. Impact of exercise and moderate hypoxia on glycemic regulation and substrate oxidation pattern. *PLoS One* 9: e108629, 2014.
70. Nishimura A, Sugita M, Kato K, Fukuda A, Sudo A, Uchida A. Hypoxia increases muscle hypertrophy induced by resistance training. *Int J Sports Physiol Perform* 5: 497–508, 2010.
71. Ottosson M, Lönnroth P, Björntorp P, Edén S. Effects of cortisol and growth hormone on lipolysis in human adipose tissue. *J Clin Endocrinol Metab* 85: 799–803, 2000.
72. Park H-Y, Jung W-S, Kim J, Lim K. Twelve weeks of exercise modality in hypoxia enhances health-related function in obese older Korean men: A randomized controlled trial. *Geriatr Gerontol Int* 19: 311–316, 2019.
73. Pascoe DD, Gladden LB. Muscle glycogen resynthesis after short term, high intensity exercise and resistance exercise. *Sports Med* 21: 98–118, 1996.
74. Peltonen JE, Tikkanen HO, Rusko HK. Cardiorespiratory responses to exercise in acute hypoxia, hyperoxia and normoxia. *Eur J Appl Physiol* 85: 82–88, 2001.
75. Peyrard A, Willis SJ, Place N, Millet GP, Borrani F, Rupp T. Neuromuscular evaluation of arm-cycling repeated sprints under hypoxia and/or blood flow restriction. *Eur J Appl Physiol* 119: 1533–1545, 2019.
76. Purvis D, Gonsalves S, Deuster PA. Physiological and psychological fatigue in extreme conditions: Overtraining and elite athletes. *PM&R* 2: 442–450, 2010.
77. Ramos-Campo DJ, Rubio-Arias JA, Dufour S, Chung L, Ávila-Gandía V, Alcaraz PE. Biochemical responses and physical performance during high-intensity resistance circuit training in hypoxia and normoxia. *Eur J Appl Physiol* 117: 809–818, 2017.
78. Ramos-Campo DJ, Rubio-Arias JÁ, Freitas TT, Camacho A, Jiménez-Diaz JF, Alcaraz PE. Acute physiological and performance responses to high-intensity resistance circuit training in hypoxic and normoxic conditions. *J Strength Cond Res* 31: 1040–1047, 2017.
79. Ramos-Campo DJ, Scott BR, Alcaraz PE, Rubio-Arias JA. The efficacy of resistance training in hypoxia to enhance strength and muscle growth: A systematic review and meta-analysis. *Eur J Sport Sci* 18: 92–103, 2018.
80. Robergs RA, Ghiasvand F, Parker D. Biochemistry of exercise-induced metabolic acidosis. *Am J Physiol Regul Integr Comp Physiol* 287: R502–R516, 2004.
81. Schiaffino S, Mammucari C. Regulation of skeletal muscle growth by the igf1-akt/pkb pathway: Insights from genetic models. *Skeletal Muscle* 1: 4, 2011.
82. Schödel J, Oikonomopoulos S, Ragoussis J, Pugh CW, Ratcliffe PJ, Mole DR. High-resolution genome-wide mapping of hif-binding sites by chip-seq. *Blood* 117: e207–e217, 2011.
83. Schreuder TH, Nyakayiru J, Houben J, Thijssen DH, Hopman MT. Impact of hypoxic versus normoxic training on physical fitness and vasculature in diabetes. *High Alt Med Biol* 15: 349–355, 2014.
84. Scortegagna M, Cataisson C, Martin RJ, et al. HIF-1alpha regulates epithelial inflammation by cell autonomous NFkappaB activation and paracrine stromal remodeling. *Blood* 111: 3343–3354, 2008.
85. Scott BR, Slattery KM, Sculley DV, Hodson JA, Dascombe BJ. Physical performance during high-intensity resistance exercise in normoxic and hypoxic conditions. *J Strength Cond Res* 29: 807–815, 2015.
86. Scott BR, Slattery KM, Sculley DV, Lockhart C, Dascombe BJ. Acute physiological responses to moderate-load resistance exercise in hypoxia. *J Strength Cond Res* 31: 1973–1981, 2017.
87. Semenza GL. Hydroxylation of hif-1: Oxygen sensing at the molecular level. *Physiology* 19: 176–182, 2004.
88. Semenza GL. Hif-1: Upstream and downstream of cancer metabolism. *Curr Opin Genet Dev* 20: 51–56, 2010.
89. Smith CM, Salmon OF, Jenkins JR. Effect of moderate and severe hypoxic exposure coupled with fatigue on psychomotor vigilance testing, muscle tissue oxygenation, and muscular performance. *Curr Res Physiol* 4: 243–251, 2021.
90. Snyder EM, Carr RD, Deacon CF, Johnson BD. Overnight hypoxic exposure and glucagon-like peptide-1 and leptin levels in humans. *Appl Physiol Nutr Metab* 33: 929–935, 2008.
91. Stitt TN, Drujan D, Clarke BA, et al. The igf-1/pi3k/akt pathway prevents expression of muscle atrophy-induced ubiquitin ligases by inhibiting foxo transcription factors. *Mol Cell* 14: 395–403, 2004.
92. Sun M, Reis DJ. Hypoxia selectively excites vasomotor neurons of rostral ventrolateral medulla in rats. *Am Journal Physiology* 266: R245–R256, 1994.
93. Takarada Y, Takazawa H, Sato Y, Takebayashi S, Tanaka Y, Ishii N. Effects of resistance exercise combined with moderate vascular occlusion on muscular function in humans. *J Appl Physiol* 88: 2097–2106, 2000.
94. Törpel A, Peter B, Schega L. Effect of resistance training under normobaric hypoxia on physical performance, hematological parameters, and body composition in young and older people. *Front Physiol* 11: 335, 2020.
95. van Doorslaer de Ten Ryen S, Warnier G, Gnimassou O, et al. Higher strength gain after hypoxic vs normoxic resistance training despite no changes in muscle thickness and fractional protein synthetic rate. *FASEB J* 35: e21773, 2021.
96. Wan JJ, Qin Z, Wang PY, Sun Y, Liu X. Muscle fatigue: General understanding and treatment. *Exp Mol Med* 49: e384, 2017.
97. Watanobe H, Habu S. Leptin regulates growth hormone-releasing factor, somatostatin, and alpha-melanocyte-stimulating hormone but not neuropeptide y release in rat hypothalamus in vivo: Relation with growth hormone secretion. *J Neurosci* 22: 6265–6271, 2002.
98. Watt MJ, Howlett KF, Febbraio MA, Spriet LL, Hargreaves M. Adrenaline increases skeletal muscle glycogenolysis, pyruvate dehydrogenase activation and carbohydrate oxidation during moderate exercise in humans. *J Physiology* 534: 269–278, 2001.
99. Wu RS. Hypoxia: From molecular responses to ecosystem responses. *Mar Pollut Bull* 45: 35–45, 2002.
100. Xie A, Skatrud JB, Puleo DS, Morgan BJ. Exposure to hypoxia produces long-lasting sympathetic activation in humans. *J Appl Physiol* 91: 1555–1562, 2001.
101. Yan B, Lai X, Yi L, Wang Y, Hu Y. Effects of five-week resistance training in hypoxia on hormones and muscle strength. *J Strength Cond Res* 30: 184–193, 2016.
102. Zacharewicz E, Della Gatta P, Reynolds J, et al. Identification of micrornas linked to regulators of muscle protein synthesis and regeneration in young and old skeletal muscle. *PLoS One* 9: e114009, 2014.
103. Zammit PS, Partridge TA, Yablonka-Reuveni Z. The skeletal muscle satellite cell: The stem cell that came in from the cold. *J Histochem Cytochem* 54: 1177–1191, 2006.