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REVIEW ARTICLE

Hypoxia and Resistance Exercise: A Comparison of Localized and Systemic Methods

Brendan R. Scott · Katie M. Slattery · Dean V. Sculley · Ben J. Dascombe

Abstract It is generally believed that optimal hypertrophic and strength gains are induced through moderate- or high-intensity resistance training, equivalent to at least 60 % of an individual's 1-repetition maximum (1RM). However, recent evidence suggests that similar adaptations are facilitated when low-intensity resistance exercise (~20–50 % 1RM) is combined with blood flow restriction (BFR) to the working muscles. Although the mechanisms underpinning these responses are not yet firmly established, it appears that localized hypoxia created by BFR may provide an anabolic stimulus by enhancing the metabolic and endocrine response, and increase cellular swelling and signalling function following resistance exercise. Moreover, BFR has also been demonstrated to increase type II muscle fibre recruitment during exercise. However, inappropriate implementation of BFR can result in detrimental effects, including petechial haemorrhage and dizziness. Furthermore, as BFR is limited to the limbs, the muscles of the trunk are unable to be trained under localized hypoxia. More recently, the use of systemic hypoxia via hypoxic chambers and devices has been investigated as a novel way to stimulate similar physiological responses to resistance training as BFR techniques. While little evidence is available, reports indicate that beneficial adaptations, similar to those induced by BFR, are possible using these methods. The use of systemic hypoxia allows large groups to train concurrently within a hypoxic chamber using multi-joint exercises. However, further scientific research is required to fully understand the mechanisms that cause augmented muscular changes during resistance exercise with a localized or systemic hypoxic stimulus.

B. R. Scott (✉) · K. M. Slattery · B. J. Dascombe
Applied Sports Science and Exercise Testing Laboratory, School of Environmental and Life Sciences, Faculty of Science and Information Technology, University of Newcastle, PO Box 127, Ourimbah, NSW 2258, Australia
e-mail: brendan.scott@uon.edu.au

K. M. Slattery
New South Wales Institute of Sport, Sydney Olympic Park, NSW 2127, Australia

D. V. Sculley
Biomedical Sciences and Pharmacy, Faculty of Health and Medicine, University of Newcastle, Ourimbah, NSW 2258, Australia

1 Introduction

Resistance exercise has a potent effect on increases in the size and strength of skeletal muscle [1]. The efficacy of a resistance training programme is determined largely by the manipulation of acute training variables, such as muscle action, loading and volume, exercise selection and order, inter-set rest periods, repetition velocity and training frequency [2]. A complex cascade of biological events occurs in response to the mechanical stimulus, including metabolic and hormonal alterations, intramuscular signalling processes, and subsequent protein synthesis [3]. For instance, local accumulation of metabolic byproducts during resistance exercise, such as lactate and hydrogen ions (H^+), stimulates the release of anabolic hormones [4–8]. These hormones in turn promote muscular hypertrophy by increasing protein synthesis and decreasing protein degradation [9–11]. Furthermore, the accumulation of metabolites may facilitate cellular swelling, and moderate subsequent signals for growth [12]. It is evident both the mechanical stress applied and methods to upregulate physiological responses should be considered when designing resistance training programmes. It may be

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possible to manipulate these physiological responses using hypoxic stimuli to accelerate strength gains from resistance exercise.

The use of a hypoxic stimulus during resistance exercise was initially studied via blood flow restriction (BFR) techniques [8, 13, 14]. More recently, devices that create a systemic hypoxic environment via nitrogen dilution or oxygen extraction have been used [15–17]. The addition of a hypoxic stimulus is suggested to increase the metabolic and hormonal responses to resistance exercise, in turn enhancing the subsequent hypertrophic and strength responses [15, 16]. However, both methods of hypoxic exposure (BFR and systemic) have inherent limitations. Therefore, the purpose of this review is to summarize the current body of literature that has reported on resistance exercise under hypoxic conditions. Current limitations of hypoxic techniques will also be examined. Where applicable, the underlying mechanisms that may facilitate strength and hypertrophic gains will be described.

2 Resistance Exercise with Blood Flow Restriction (BFR)

The BFR technique involves application of a tourniquet [14], inflatable cuff [18] or elastic knee wraps [19] around the proximal end of a limb to occlude distal blood flow, thus inducing a localized hypoxic environment during exercise [20]. Early research utilized occlusive pressures in excess of 200 mmHg [8], although more recent findings have demonstrated beneficial results with pressures as low as 50 mmHg [21]. Numerous factors can affect the acute responses to BFR resistance exercise, including the occlusive pressure used, cuff location, width and type, exercise intensity, volume and inter-set rest periods, as well as the frequency and duration of training, and whether exercise is performed to volitional fatigue or not. Training with BFR (also known as Kaatsu training) is currently promoted as a novel training method that enhances muscle hypertrophy and strength [22]. While the American College of Sports Medicine typically recommends that resistance training intensity exceed 60 % 1-repetition maximum (1RM) to induce optimum hypertrophy [23], numerous studies have demonstrated substantial increases in hypertrophy and strength following 2–16 weeks of BFR training at intensities as low as 20 % 1RM [21, 24–26]. Although the precise mechanisms are not yet clear, the augmented responses to resistance exercise with BFR are believed to be accounted for by a greater accumulation of metabolites and concomitant increases in anabolic hormone concentrations, intramuscular signalling, intracellular swelling and motor unit recruitment [8, 12, 18]. The following sections of this review will detail the adaptive and perceptual responses, potential causative mechanisms, as well as the practical applications of BFR training.

2.1 Adaptive and Perceptual Responses to BFR Training

2.1.1 Morphological Adaptations

Several researchers have observed increased muscle cross-sectional area (CSA) following BFR training [13, 24–28]. Takarada et al. [13] reported that 16 weeks of low-intensity (~50–30 % 1RM) elbow flexion training (twice per week) with BFR elicited greater increases in muscle CSA in older women than low-intensity training alone. More recently, Manimmanakorn et al. [29] observed that the CSA of knee extensors and flexors increased by 6.6 ± 4.5 % (mean ± SD) following 5 weeks of low-intensity (20 % 1RM) BFR training in netball athletes, whereas the CSA increased by 2.9 ± 2.7 % in the control group. While many of these investigations recruited participants with little or unspecified resistance training experience, recent research indicates that BFR exercise may also be beneficial for resistance-trained athletic populations [30–32]. Low-intensity (20 % 1RM) resistance exercise combined with BFR has resulted in greater hypertrophy than in non-restricted control groups in track and field athletes [30], and American football players [31]. As these participants already have achieved a high level of muscular adaptation to resistance training, low-intensity resistance training would not normally have facilitated hypertrophic gains. Therefore, the addition of BFR during resistance exercise appears to also benefit skeletal muscle adaptation in resistance-trained athletes.

2.1.2 Increases in Muscular Strength

Several authors have reported increased peak torque and maximal rate of torque development across a range of angular velocities following low-intensity (20–50 % 1RM) BFR training, despite no significant changes in control groups performing the equivalent training without BFR [13, 14, 25, 26]. These increases in strength are likely due to concomitant increases in muscle fibre CSA and neural adaptations. While general strength is largely dependent upon muscle CSA and contractile properties [33], low-intensity resistance exercise with BFR has also been reported to increase muscle fibre recruitment during exercise [8, 25, 34–36]. Numerous investigations have noted that neural drive, measured via the amplitude of muscle electromyography (EMG) signals, is increased following a period of traditional resistance training [37]. As neural adaptations are predominant in strength gains during the early stages of resistance training [38], it is possible that

strength gains in untrained subjects following BFR training are partly explained by neuromuscular adaptation, which may be augmented by consistent increases in muscle recruitment. However, it should be acknowledged that low-intensity BFR resistance exercise does not increase muscle activation to the same degree as higher-intensity resistance exercise without BFR [39, 40]. Therefore, it is likely that neural adaptations following BFR are dissimilar to those experienced following traditional high-intensity resistance training.

Low-intensity BFR training has also been shown to elicit significant increases in maximal isometric strength, and muscular endurance across 50 repeated submaximal contractions compared with low-intensity resistance training without BFR [25]. This increase in muscular endurance may reflect intramuscular metabolic adaptations (i.e. increases in oxidative energy metabolism and H^+ buffering) rather than increased neural fatigue resistance. In support of this suggestion, no changes were present in the integrated EMG pattern during the initial or the last 10 of the 50 repeated contractions [25].

2.1.3 *Perceptual Responses*

Perceptual responses to resistance exercise are important for monitoring and regulating exercise intensity, providing general markers of the physiological demands during training. Generally, it appears that resistance exercise with BFR results in rating of perceived exertion (RPE) values similar to the equivalent exercise without BFR [21, 41, 42]. However, in a recent study that used knee wraps to occlude blood flow, subjects reported significantly greater RPE scores following low-intensity knee extension to failure with BFR than without [43]. Furthermore, contrasting data have been reported relating to perceived pain during BFR resistance exercise. Some authors have reported that pain was similar between BFR and the control groups, following low-intensity resistance exercise to exhaustion [29, 41], while others observed significantly greater pain scores following low-intensity resistance exercise with BFR than without [42, 43]. These conflicting data might be explained by differences in the method used to restrict blood flow (i.e. narrow elastic knee wraps vs. inflatable cuffs), the occlusive pressure used, and the width of the occlusive cuffs [41, 44, 45].

2.2 Potential Mechanisms of BFR for Hypertrophy and Strength

2.2.1 *Concentration of Metabolites*

The anabolic response to exercise-induced metabolic stress is well documented (for a review see Schoenfeld [46]). Research suggests that when resistance exercise is performed with BFR, a significantly greater metabolic stress is observed via exaggerated phosphocreatine (PCr) depletion [47, 48], increased inorganic phosphate (P_i) [48, 49], pH decreases [47, 48], and increased lactate production [8, 18, 50–52]. In an early investigation, Takarada et al. [8] examined the physiological responses to five sets of bilateral leg extensions (20 % 1RM) to exhaustion, either with or without BFR. Immediately post-exercise, plasma lactate concentration was doubled in the BFR group compared with the control [8]. More recently, Suga et al. [47] reported that low-intensity plantar flexion exercise (3 sets of 30 repetitions at 20 % 1RM) with BFR resulted in a similar metabolic stress (namely intramuscular metabolites and pH) when compared with high-intensity (65 % 1RM) exercise without BFR. Furthermore, increases with muscle CSA following BFR training have been strongly correlated to metabolic stress, measured via increases in the P_i ($r = 0.87$) and decreases in pH ($r = 0.60$) [49]. Taken together, these findings suggest that the decreased availability of oxygen to the working muscles during BFR increases the reliance on anaerobic metabolism [53], and restricts lactate clearance. This augmented metabolic response to resistance exercise with BFR may potentially lead to greater type II muscle fibre recruitment, hormonal responses, intramuscular signalling and intracellular swelling [46].

2.2.2 *Hormonal Responses*

Hormones play an integral role in regulating the anabolic responses to resistance exercise [54]. Elevated concentrations of hormones such as growth hormone (GH), insulin-like growth factor (IGF)-1 and testosterone increase the likelihood of hormone receptor interactions that promote anabolic processes [11]. Generally, investigations have reported an augmented hormonal response to performing resistance exercise under BFR conditions [8, 15, 16, 52]. Several researchers have reported significantly greater plasma GH concentrations following resistance exercise with BFR than without [8, 18, 26, 50, 52, 55]. In their seminal study, Takarada et al. [8] reported GH elevations of $\sim$290 times greater than baseline after BFR trials, without any significant increase in the control group exercising without BFR. Furthermore, three sets of low-intensity (30 % 1RM) resistance exercise with BFR facilitated a fourfold increase in GH, despite no significant rise following moderate-intensity exercise (70 % 1RM) without BFR [50]. The GH response to low-intensity resistance exercise with BFR appears to provide a significant anabolic stimulus, potentially even greater than traditional resistance exercise designed to promote hypertrophy using much higher intensities ($\sim$70 % 1RM) without BFR [23, 56].

Many of the anabolic actions of GH are mediated by IGF-1 [11, 57], which is predominantly synthesized and released in response to circulating GH levels [58]. Some research has reported upregulated IGF-1 responses to acute bouts of low-intensity BFR resistance exercise [18] and to high-frequency BFR training (twice daily) [24], which are similar in magnitude to typical responses following high-intensity resistance training without BFR [59, 60]. However, despite noting enhanced GH responses following low-intensity (20 % 1RM) resistance exercise with BFR, neither Fujita et al. [51] or Patterson et al. [55] observed concomitant increases in IGF-1. This discrepancy may be explained by the different time course of change in GH and IGF-1 [57], with peaks in IGF-1 typically occurring at 16–28 h following GH release [57, 61]. While it is likely that the high-frequency BFR training employed by Abe et al. [24] resulted in chronically elevated GH levels and concurrent increases in IGF-1, it is unclear at this time what mechanisms may have facilitated the higher IGF-1 levels following a single bout of resistance exercise with BFR.

Testosterone has anabolic effects on skeletal muscle directly by increasing protein synthesis and decreasing protein degradation, and indirectly by stimulating other anabolic hormones [11]. However, low-intensity resistance exercise with BFR appears not to augment testosterone responses [50, 51]. These results may be explained by the low volume and/or intensity of the exercise protocols used, which might have been insufficient to elicit changes in testosterone levels. Significant increases in testosterone have previously been demonstrated following non-restricted multi-joint resistance training of considerably higher volume and intensity [62]. This suggests that the magnitude of testosterone responses might not be affected by the degree of metabolic stress during resistance exercise [5, 63], but rather by factors such as the amount of muscle mass stimulated, and the intensity and volume of exercise [64].

The actions of GH and testosterone are enhanced by catecholamines, which reflect the acute demands of exercise, and influence force production, muscle contraction rate and energy availability [65–67]. Research has reported low-intensity resistance exercise with BFR to increase norepinephrine secretion, in concert with GH and lactate levels, more than without BFR [8, 18]. However, the relationship between GH and norepinephrine levels was not significant [18]. It is therefore likely that a combination of anaerobic factors such as local ischaemia and accumulation of lactate and H^+ ions may stimulate peripheral afferent neural activity, resulting in an enhanced GH-releasing hormone secretion and/or inhibition of somatostatin release from the hypothalamus [18, 66, 68]. As such, despite the moderating effect that catecholamines may have on other anabolic hormones, their exact role during BFR exercise is not yet fully understood.

Cortisol is released from the adrenal cortex in response to stress during exercise [15], and promotes catabolism via decreased protein synthesis and increased protein degradation [57]. The cortisol response to resistance exercise appears to be dependent on the stress and metabolic requirements of the exercise [5, 69]. Fujita et al. [51] reported an increase in serum cortisol after low-intensity resistance exercise with BFR, despite no changes in the control condition, possibly reflecting additional stress from BFR. In contrast, Reeves et al. [50] observed no significant change in serum cortisol in any experimental conditions. Cortisol responses to exercise primarily occur following high-intensity exercise, possibly due to congruous anaerobic metabolic factors [70]. Thus, these conflicting findings may reflect differences in the exercise protocols, particularly the short 30 s inter-set rest period used by Fujita et al. [51].

In general, low-intensity resistance exercise combined with BFR promotes a favourable anabolic endocrine response, similar to traditional training programmes designed to promote hypertrophy [56]. However, while GH appears to be the primary hormone affected by BFR, the direct influence of GH on strength gains remains equivocal [68]. Indeed, the role of systemic endocrine responses in resistance training adaptation has been a point of conjecture in recent years, with some proposing that there is no evidence to suggest transient exercise-induced changes in GH have anabolic effects in healthy individuals [71]. West et al. [72] contend that exercise-mediated hypertrophy is in fact an intrinsic process dependent on intramuscular signalling, rather than systemic increases in anabolic hormones. Therefore, it must be acknowledged that systemic hormones and growth factors may not be as important for protein synthesis as once thought. Beneficial adaptive responses to BFR training may therefore be moderated by other factors in addition to an increased endocrine response.

2.2.3 Intramuscular Signalling

Recent evidence suggests that improvements in muscular size and strength following low-intensity resistance training (20 % 1RM) with BFR rely considerably on the proliferation and differentiation of myogenic stem cells, resulting in the addition of myonuclei to the exercised fibres [73]. Mechanical deformation of muscle fibres during contractile processes and stretching also stimulate intramuscular signalling pathways independently of hormones and growth factors [74]. In particular, mechanical disruptions activate the mammalian target of rapamycin (mTOR) pathway, which moderates the adaptive responses

via translation initiation and muscle protein synthesis (MPS) [75]. mTOR signalling increases MPS by enhancing translational efficiency [i.e. messenger RNA (mRNA) translated per ribosome] [3], and is therefore critical for subsequent skeletal muscle hypertrophy [76]. Fujita et al. [51] observed increased phosphorylation of ribosomal S6 kinase 1 (S6K1; a key downstream regulator of the mTOR signalling pathway), as well as significantly higher MPS at 3 h post-exercise in the BFR condition, despite no change in the control. More recently, Fry et al. [77] reported increases in both MPS and S6K1 phosphorylation 3 h after four sets of low-intensity (20 % 1RM) bilateral knee extensions with BFR, despite no change following equivalent trials without BFR. Similarly, Wernbom et al. [78] reported enhanced mTOR signalling 1 h following low-intensity unilateral knee extensions to failure (30 % 1RM) in a BFR condition and not in a non-occluded control. The authors concluded that enhanced mTOR signalling could partly explain the augmented hypertrophic response induced by low-intensity resistance exercise with BFR. However, Wernbom et al. [78] noted that while mTOR signalling was also enhanced at 24 h following exercise, there was no difference between conditions. It is therefore difficult to assess the relative contributions of mTOR signalling in concurrence with growth factors and systemic responses [79].

Reactive oxygen species (ROS) production presents another novel mechanism that may mediate the adaptive responses to BFR training. While chronically elevated levels of ROS have been implicated in harmful biological events, acute production of ROS is important for optimum cellular function and development [80, 81]. Previously, ROS have been shown to promote growth in both smooth and cardiac muscle [82], and it is theorized that similar hypertrophic effects may occur in skeletal muscle [13, 41, 83]. However, while the activity of ROS within muscle is known to increase in ischaemic conditions, particularly upon reperfusion [84], previous research by Takarada et al. [8] reported no change in lipid peroxide levels following low-intensity resistance exercise either with or without BFR. Similar findings were reported by Goldfarb et al. [85], who observed no significant increase in markers of oxidative stress (glutathione status and plasma protein carbonyls) following low-intensity (30 % 1RM) resistance exercise with BFR, despite increases following both moderate-intensity (70 % 1RM) resistance exercise without BFR, and BFR alone. As such, further research is required to investigate whether markers of redox signalling and exercise-induced ROS production are augmented by the addition of BFR, and if ROS play a role in subsequent cellular signalling processes for post-exercise muscle adaptations [64].

Contrary to the potential anabolic effects of augmented mTOR signalling and ROS production, myostatin acts as a negative regulator of skeletal muscle growth [86]. Decreased expression of myostatin in response to resistance exercise has been noted in several investigations [87–91], and is necessary for optimal hypertrophic adaptation [88]. Reductions in myostatin mRNA were reported by Drummond et al. [92] following low-intensity resistance exercise with BFR. Similarly, Laurentino et al. [93] demonstrated that myostatin mRNA expression was significantly decreased following 8 weeks of low-intensity (20 % 1RM) resistance training with BFR and high-intensity (80 % 1RM) training without BFR. These findings support previous research that investigated partial BFR in a rat model [94]. However, Drummond et al. [92] reported similar reductions in myostatin mRNA in the non-occlusive control group, indicating that the reduced myostatin was unlikely to be solely mediated by BFR. Furthermore, Manini et al. [95] failed to detect any differences in myostatin mRNA levels following four sets of bilateral knee extension exercise at 20 % 1RM either with or without BFR. These contrasting findings suggest significant reductions in myostatin expression may require prolonged BFR training, rather than a single exposure [64].

2.2.4 Intracellular Swelling

Intracellular swelling is a novel mechanism that has been proposed by numerous authors to mediate anabolic responses to resistance exercise with BFR [12, 46, 96, 97]. Cell swelling is maximized in exercise that relies heavily on anaerobic metabolism, due to the osmotic changes caused by lactate accumulation [98]. The localized hypoxic environment created by BFR increases the production of metabolites, while the occlusion itself limits venous outflow which promotes further metabolite accumulation [12]. Thus, a resultant increase in the flow of water into the cell is required to equilibrate the osmotic gradient [12].

Research has demonstrated that hydration-mediated cellular swelling increases protein synthesis and decreases proteolysis in hepatocytes, osteocytes, breast cells and muscle fibres [99]. With respect to muscle, it is proposed that cell swelling may trigger the proliferation of satellite cells and facilitate their fusion to hypertrophying muscle fibres [100]. Increased pressure against the cytoskeleton or cellular membrane caused by swelling may be perceived to threaten cellular integrity, causing the cell to initiate a signalling response to reinforce its ultrastructure [46, 54, 101]. It is suggested that this transient increase in muscle cell volume could activate anabolic signalling cascades, such as mTOR and mitogen-activated protein kinase (MAPK) pathways [12, 46, 54], which are known to be

stimulated by low-intensity resistance exercise with BFR [51, 77].

However, it should be noted that evidence in opposition to the cell swelling theory has recently been presented. Gundermann et al. [102] compared low-intensity resistance exercise (20 % 1RM) with hyperaemia simulated via pharmacological vasodilation against the equivalent exercise with BFR. Increases in mixed muscle fractional synthetic rate, and phosphorylation of mTOR, S6K1 and extracellular signal-regulated kinases were observed in the BFR trials, but not in the vasodilation group. However, the initial hyperaemic response to pharmacological vasodilatation (first 10 min) did not replicate that observed following BFR exercise, and possibly did not reach a threshold required to stimulate significant anabolic signalling. In addition, while decreased proteolysis may enhance net protein accretion during cellular swelling [46], this was not measured. Therefore, while there is a paucity of research that has examined the mechanisms by which cellular swelling may promote adaptation to resistance exercise with BFR, this novel mechanism warrants future research attention.

2.2.5 *Muscle Fibre Recruitment*

Several investigations have reported increased levels of muscle activation during resistance exercise with BFR using surface EMG [8, 34–36]. Originally, Takarada et al. [8] reported that the BFR trial facilitated 1.8 times greater muscle stimulation than the control, despite no difference in the force generated and the mechanical work produced. This enhanced muscle activation at low levels of force generation may relate to a hypoxic intramuscular environment, where low-threshold type I motor units will readily fatigue, requiring activation of more glycolytic (i.e. type II) motor units to maintain the same level of force generation [103, 104]. The size principle suggests that type I fibres are recruited first, with type II fibres being recruited with increasing exercise intensities [105]. Given that the hypoxic condition and metabolite accumulation which occur during BFR exercise can stimulate group III and IV afferents [106–108], mechanistically speaking, a reflexive net inhibitory effect on the α-motor neuron may result [109], facilitating increased fibre recruitment to maintain force and protect against conduction failure [106, 107]. Therefore, the potential for hypertrophic and strength gains may be augmented by BFR, even at very low training intensities, due to the increased recruitment of type II motor units.

However, it must be acknowledged that some investigations have failed to demonstrate increased muscle activation during resistance exercise with BFR. Both Wernbom et al. [41] and Kacin and Strazar [28] have reported similar EMG patterns between BFR and control conditions during low-intensity [30 % 1RM and 15 % maximum voluntary contraction (MVC), respectively] unilateral knee extension. Importantly, participants in these investigations exercised to volitional fatigue in both BFR and non-restricted conditions, suggesting that BFR does not increase muscle activation above non-restricted levels when exercise is performed to failure. While increased motor unit activation is likely to contribute strongly to enhanced morphological adaptations following BFR training [106], other factors related to the occlusive stimulus are also likely to play a role. Indeed, research suggests that low-intensity BFR resistance exercise does not facilitate muscle activation of the same magnitude as higher-intensity resistance exercise without BFR, when performed to volitional fatigue [39, 40]. As such, it is unlikely that low-intensity BFR resistance exercise will stimulate the complete pool of high-threshold motor units, resulting in chronic neuromuscular responses dissimilar to those experienced following high-intensity training without BFR. Table 1 provides a summary of the potential mechanisms underpinning BFR resistance exercise discussed in this section.

2.3 Practical Applications and Limitations of BFR

The muscular adaptations to BFR training may benefit populations such as the elderly or post-surgery rehabilitation patients that exhibit compromised strength and/or joint stability [79]. Low-intensity training combined with BFR could reduce joint articular and ligament stress forces when compared with higher intensity resistance training (>60 % 1RM), decreasing the incidence of injury whilst still promoting strength and hypertrophic increases [13, 14, 25]. Furthermore, low-intensity BFR training does not require extensive recovery time between training sessions [110] due to the low mechanical stress and reduced muscle damage and inflammation [8]. It may therefore be possible to employ higher training frequencies than traditional resistance training programmes [24].

While BFR training appears beneficial for facilitating hypertrophic and strength gains, it is important to recognize its limitations. Evidence suggests that low-intensity resistance exercise with BFR results in lower motor unit recruitment than higher-intensity exercise without BFR, therefore providing a lesser neurological stimulus [39, 40]. It is also possible that while low-intensity resistance exercise with BFR can result in increased strength and CSA of skeletal muscle, a concomitant increase in the strength of connective tissues may not occur due to the decreased mechanical loading. The possibility exists that the strength of muscle and connective tissues will adapt disproportionately to BFR resistance training, increasing

Table 1 Summary of the current understanding of physiological responses to resistance exercise with BFR, and factors influencing the magnitude of these responses

Mechanism	Responses (when compared with the equivalent training without BFR)	Potential factors influencing the magnitude of responses
Metabolic stress	↑ [BLa^-]	Inter-set recovery period
	↑ PCr depletion	Occlusion maintained during inter-set recovery
	↑ P_i	Occlusive pressure used (i.e. degree of vascular occlusion)
	↓ pH	
Hormonal responses	↑ GH	The degree of metabolic stress associated with exercise
	↔ testosterone	Amount of muscle mass recruited during exercise
	? IGF-1	
	? catecholamine	
	? cortisol	
Intramuscular signalling	↑ phosphorylation of S6K1 (mTOR signalling)	Mechanical stress applied (volume and intensity)
	↑ proliferation and differentiation of satellite cells	Level of muscular ischaemia
	↔ ROS	
	↔ myostatin	
Intracellular swelling	? cell swelling stimulates intrinsic volume sensors	Degree of occlusion and subsequent venous pooling
	? cell swelling triggers anabolic signalling and MPS	Metabolic stress associated with exercise
Muscle fibre recruitment	↑ motor unit activation	Degree of metabolic stress associated with exercise
	↓ motor unit activation when compared with high-intensity exercise without BFR	Possibly no effect when exercise is performed to failure
Reactive hyperaemia	↑ blood flow to muscles following cuff release	Level of muscular ischaemia
	? MPS	Magnitude of hyperaemia likely affects signalling and MPS

BFR blood flow restriction, [*BLa^-*] blood lactate concentration, *PCr* phosphocreatine, *P_i* inorganic phosphate, *GH* growth hormone, *IGF-1* insulin-like growth factor-1, *S6K1* ribosomal S6 kinase 1, *mTOR* mammalian target of rapamycin, *ROS* reactive oxygen species, *MPS* muscle protein synthesis, *CSA* cross-sectional area, ↓ decrease, ↑ increase, ↔ no significant change, *?* equivocal or currently unknown response

the likelihood of musculotendinous injury if heavy exercise loads are subsequently used.

The logistics of using BFR cuffs with large groups of individuals across a range of exercises may prove impractical, due to equipment and expertise requirements. While the use of elastic wraps to occlude blood flow may simplify BFR application [20], the occlusive pressure is difficult to monitor with this technique. Importantly, without abundant experience, petechial haemorrhage beneath the skin, chills, numbness and dizziness can result from inappropriately applying cuffs or elastic wraps [22]. Additionally, as BFR is limited to the limbs, muscles of the trunk are unable to be trained under localized hypoxic conditions [17]. Although recent evidence suggests that hypertrophic responses are possible in non-occluded muscles following BFR training [24, 111, 112], the relationship between limb and trunk hypertrophy was not significant ($r = 0.54$; $p = 0.13$) [112]. Further research is required before the efficacy of BFR training for increasing the size and strength of the trunk muscles can be established. To overcome these limitations, the use of systemic hypoxia via simulated altitude instead of BFR may provide an attractive alternative for many individuals. Figure 1 presents a simplified flowchart of the interplay between well-understood and proposed mechanisms that may affect adaptations to BFR resistance exercise and intermittent hypoxic resistance training.

3 Resistance Exercise with Systemic Hypoxia

Intermittent hypoxic training, whereby the amount of oxygen available in inspired air is reduced during training, has been shown to improve both aerobic [113] and anaerobic [114] performance in athletes. Enhanced metabolic function (i.e. molecular and structural adaptations favouring oxygen transport and utilization) has also been demonstrated following high-intensity cycling training in hypoxia, compared with training in normoxia [115, 116], with muscle adaptations being dependent on the degree of hypoxia and the duration of exposure [117]. Given that the localized hypoxic environment created by BFR enhances both acute [8, 18, 50, 51] and adaptive [21, 24, 25, 36] responses to resistance exercise, it is plausible that similar benefits may result from performing resistance exercise in systemic hypoxia [29]. Researchers have recently begun to investigate the use of hypoxic devices, which typically provide a systemic normobaric hypoxic environment via

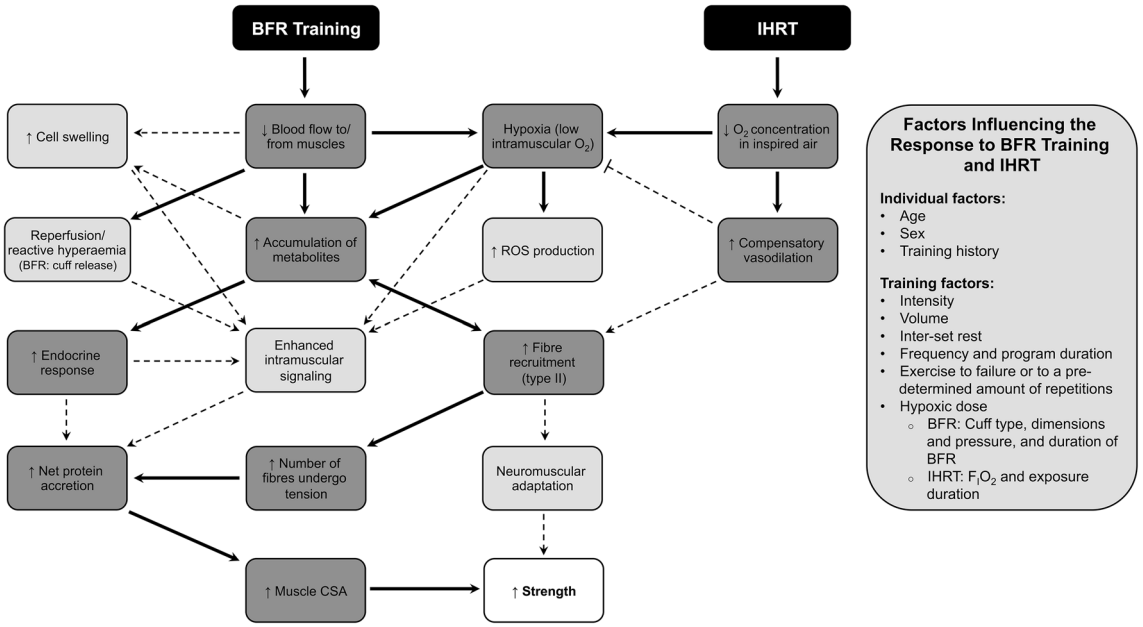

Fig. 1 Simplified schematic of the proposed interplay between potential mechanisms that may mediate the adaptive responses to BFR training and IHRT. Likely mechanisms are represented by *dark shaded boxes*, whereas possible mechanisms that require further research are represented by *light shaded boxes*. Outcomes of training are represented by *white boxes* with *bold* text. *Bold arrows* indicate a likely link between proposed mechanisms, and *dotted arrows* indicate a possible link requiring further investigation. *Blunted arrow heads* indicate an inhibitory effect. *Note*: While increased muscle CSA is represented here as a mechanism underpinning increases in strength, it may also be considered as a training outcome if hypertrophy is the desired goal. *BFR* blood flow restriction, *IHRT* intermittent hypoxic resistance training, O_2 oxygen, *ROS* reactive oxygen species, *CSA* cross-sectional area, F_IO_2 fraction of inspired oxygen, ↑ increase, ↓ decrease

nitrogen dilution or oxygen extraction [118]. This allows trunk musculature to be trained under hypoxic conditions with the limbs, providing a novel training strategy for individuals requiring development of these muscles [17]. For the purpose of this review, bouts of resistance training completed with a systemic hypoxic stimulus will be termed intermittent hypoxic resistance training (IHRT). While the combination of localized hypoxia (via BFR) and resistance exercise has been found to induce beneficial muscular responses [8, 13, 18, 21, 24–28, 52], few studies to date have examined the physiological responses to IHRT (Tables 2 and 3). The following sections of this review will report on the adaptive and perceptual responses following IHRT, before discussing the suggested mechanisms that might underpin these responses.

3.1 Adaptive and Perceptual Responses to Intermittent Hypoxic Resistance Training (IHRT)

3.1.1 Morphological Responses

Few researchers have detailed the morphological responses to IHRT using systemic hypoxia. In an early study, Friedmann et al. [120] reported that 4 weeks of low-intensity (30 % 1RM) knee extension exercise in a normobaric hypoxic environment [fraction of inspired oxygen (F_IO_2) = 0.12] did not induce significant gains in muscle or fibre CSA. However, no significant gains were made in the control group either, suggesting that the low-intensity resistance training in systemic hypoxia was not superior to equivalent normoxic training. In contrast, Manimmanakorn et al. [29] reported that 5 weeks of low-intensity (20 % 1RM) IHRT elicited greater increases in the combined CSA of the knee extensor and flexor muscles than the equivalent training in normoxia [6.1 ± 5.1 vs. 2.9 ± 2.7 % (mean ± SD), respectively] in female netball athletes. Interestingly, similar gains were observed in the CSA of subjects who performed training with BFR (6.6 ± 4.5 %) [29]. Nishimura et al. [17] also reported significant increases in the CSA of the elbow flexors and extensors of untrained males after 6 weeks of moderate-intensity resistance training (70 % 1RM) in hypoxia (F_IO_2 = 0.16), despite no significant morphological changes after equivalent training in normoxia.

The discrepancy between these investigations may be accounted for by the training programme durations. Friedmann et al. [120] trained participants for 4 weeks, whereas Nishimura et al. [17] and Manimmanakorn et al. [29] trained participants for 6 and 5 weeks, respectively. Additionally, while Friedmann et al. [120] and Manimmanakorn et al. [29] employed similar low-intensity loads and repetition schemes, the inter-set recovery period varied

Table 2 Summary of research examining the acute responses to resistance exercise with systemic hypoxia

Study	Subjects	Testing protocol				Physiological/physical response	Main findings
		Hypoxic dose	Exercise (intensity)	Sets × reps (inter-set rest; s)	Control group		
Kon et al. [15]	Healthy males ($n = 14$)	Acute hypoxia ($F_IO_2 = 0.13$); including 15 min pre-exercise and 60 min post-exercise	Bench press and leg press (70 % 1RM)	5 × 10 (60)	Normoxia	↓ arterial and muscle oxygen saturation Greater ↑ [BLa^-] after hypoxic condition ↑ GH release at 15 and 30 min post-exercise after hypoxic condition only ↔ epinephrine and norepinephrine (although a trend for higher values after hypoxic condition)	Moderate-intensity resistance exercise in hypoxic conditions can induce greater accumulation of metabolites and a stronger anabolic hormone response than equivalent training in normoxia
Etheridge et al. [126]	Healthy males ($n = 7$)	Extended acute hypoxia ($F_IO_2 = 0.12$); 1 h pre-exercise and until 3.5 h exposure	Isometric knee extension (70 % MVC)	8 × 6 (120)	Normoxia	↔ peak MVC in hypoxia and normoxia ↑ MPS 2.5 h following resistance exercise in normoxia, but not hypoxia Linear relationship between MPS 2.5 h after resistance exercise in hypoxia and mean arterial blood O_2 saturation during hypoxia ($r^2 = 0.49$)	MVC is unchanged in hypoxia 3.5 h hypoxic exposure blunts MPS following resistance exercise Suppression of MPS correlates with blood O_2 saturation levels
Kon et al. [16]	Healthy males ($n = 8$)	Acute hypoxia ($F_IO_2 = 0.13$); including 15 min pre-exercise and 30 min post-exercise	Bench press and leg press (50 % 1RM)	5 × 14 (60)	Normoxia	↓ arterial and muscle O_2 saturation ↑ [BLa^-] (although no difference between groups) ↑ GH release at 0 and 15 min post-exercise after hypoxic condition only No difference in subjective fatigue between conditions ↔ epinephrine, norepinephrine and cortisol in either condition	Low-intensity resistance exercise in hypoxic conditions induced a greater GH response and a trend for increased accumulation of metabolites than equivalent training in normoxia, despite no change in subjective fatigue between conditions

reps repetitions, F_IO_2 fraction of inspired oxygen, *1RM* 1-repetition maximum, [BLa^-] blood lactate concentration, *GH* growth hormone, *MVC* maximal voluntary contraction, *MPS* muscle protein synthesis, O_2 oxygen, ↑ increase, ↓ decrease, ↔ no significant change

(60 and 30 s, respectively). At such low intensities, it is likely that 60 s recovery between sets is sufficient for the removal of metabolites, thus limiting the metabolic and hormonal responses, and subsequent morphological changes. Taken together, these data suggest that IHRT may provide benefits for skeletal muscle hypertrophy beyond those achieved by training in normoxia, and similar to previously described BFR techniques. Future research is required to examine the effect of varying exercise intensities, inter-set recovery periods, as well as the level of hypoxia and duration of exposure, on morphological adaptations to resistance training.

Table 3 Summary of research examining the morphological and strength responses to resistance training programmes with systemic hypoxia

Study	Subjects	Training protocol						Physiological/physical response	Main findings
		Training conditions	Hypoxic dose	Exercise (intensity)	Sets × reps (inter-set rest; s)	Frequency (sessions/ week)	Protocol duration (days)		
Friedmann et al. [120]	Untrained males ($n = 19$)	IHRT	$F_IO_2 = 0.12$/ ~4,500 m (only during training)	Unilateral knee extension (30 % 1RM)	6 × 25 (60)	3	28	↔ maximal isokinetic strength in both groups ↔ muscle CSA in both groups ↑ strength endurance capacity in both groups (not different between groups) ↔ muscle fibre-type parameters	Low-intensity resistance exercise in hypoxia did not induce greater ↑ in strength or hypertrophy
		RT	~120 m	Unilateral knee extension (30 % 1RM)	6 × 25 (60)	3	28		
Nishimura et al. [17]	Untrained males ($n = 14$)	IHRT	$F_IO_2 = 0.16$ (30 min exposure pre- and post-training)	Bilateral elbow extension and flexion (70 % 1RM)	4 × 10 (60)	2	42	↑ in muscle CSA only after IHRT ↑ 1RM after 3 weeks only following IHRT ↑ 1RM after 6 weeks in both groups No between-group differences in RPE at any stage	Moderate-intensity IHRT induced greater hypertrophic gains and faster strength increases than the training in normoxia, despite no differences in RPE
		RT	$F_IO_2 = 0.21$	Bilateral elbow extension and flexion (70 % 1RM)	4 × 10 (60)	2	42		
Manimmanakorn et al. [29]	Female netball athletes ($n = 30$)	BFR	BFR (160–230 mmHg)	Bilateral knee extension and flexion (20 % 1RM)	6 × to failure (30)	3	35	Greater ↑ MVC_3 after IHRT than RT Greater ↑ MVC_{30} after IHRT and BFR than RT Greater ↑ maximum Rep_{20} after IHRT and BFR than RT Substantially greater ↑ in CSA following IHRT and BFR than RT ↑ Perceived muscle pain during days 4–8 in IHRT than BFR and RT Greater ↑ netball-specific performance following IHRT and BFR than RT (possibly greater ↑ after BFR than IHRT)	Low-intensity IHRT facilitated greater improvements in muscle strength and size than training in normoxia, which translated into improved sport-specific performance. However, differences in sport-specific performance between IHRT and BFR groups are not understood
		IHRT	Not stated (SpO_2 maintained at ~80 %)	Bilateral knee extension and flexion (20 % 1RM)	6 × matched with BFR (30)	3	35		
		RT	Ambient air	Bilateral knee extension and flexion (20 % 1RM)	6 × matched with BFR (30)	3	35		

Table 3 continued

Study	Subjects	Training protocol						Physiological/physical response	Main findings
		Training conditions	Hypoxic dose	Exercise (intensity)	Sets × reps (inter-set rest; s)	Frequency (sessions/ week)	Protocol duration (days)		
Manimmanakorn et al. [121]	Female netball athletes ($n = 30$)	BFR	BFR (160–230 mmHg)	Bilateral knee extension and flexion (20 % 1RM)	6 × to failure (30)	3	35	Moderate effect for ↑ RMS during MVC_3 for BFR versus IHRT and RT (0.80) Moderate effect for ↑ RMS during MVC_{30} for BFR versus IHRT (0.50), and small effect for BFR versus RT (0.30) Moderate effect for ↓ RMS during Rep_{20} for RT versus BFR and IHRT (0.50 and 0.60, respectively)	Low-intensity IHRT resulted in neuromuscular adaptation, evidenced via increased RMS during MVC_3 and MVC_{30}. Improved performance during Rep_{20} following BFR and IHRT was likely due to improved contractile efficiency
		IHRT	Not stated (SpO_2 maintained at ~80 %)	Bilateral knee extension and flexion (20 % 1RM)	6 × matched with BFR (30)	3	35		
		RT	Ambient air	Bilateral knee extension and flexion (20 % 1RM)	6 × matched with BFR (30)	3	35		

The study of Pesta et al. [119] was not included in this table as morphological and strength response data were not presented

reps repetitions, *IHRT* intermittent hypoxic resistance training, *RT* resistance training without blood flow restriction in normoxia, *BFR* blood flow restriction, F_IO_2 fraction of inspired oxygen, *1RM* 1-repetition maximum, *CSA* cross-sectional area, *RPE* rating of perceived exertion, MVC_3 3 s maximum voluntary contraction, MVC_{30} 30 s maximum voluntary contraction, Rep_{20} maximum number of repetitions at 20 % 1RM, *RMS* root mean square of electromyography signal, SpO_2 arterial oxygen saturation, ↑ increase, ↓ decrease, ↔ no significant change

3.1.2 Increases in Muscular Strength

Increases in muscular strength following IHRT have recently been reported using both isotonic [17] and isokinetic [29] training models. Nishimura et al. [17] reported that muscle strength increased significantly after only 3 weeks of IHRT, whereas a significant increase in strength in the control (normoxia) group took 6 weeks. Likewise, Manimmanakorn et al. [29] observed substantially greater increases in strength (3 s MVC) and muscular endurance (30 s MVC and number of repetitions to failure at 20 % 1RM), following 5 weeks of training in the IHRT group than a normoxic control group. Similar results were presented in a subsequent study [121], with a small effect (0.44) for IHRT versus the control condition for 3 s MVC, and moderate effects (0.64 and 0.70) for 30 s MVC and number of repetitions to failure at 20 % 1RM between these conditions, respectively. While these data suggest that IHRT can accelerate increases in muscle strength, Friedmann et al. [120] observed no significant changes in maximum strength or muscular endurance following such a programme. However, this is likely explained by variations in the training dose discussed in Sect. 3.1.1.

An interesting aspect of the study by Manimmanakorn et al. [29] was the inclusion of sport-specific tests to determine whether adaptive responses to IHRT translated into improved performance. IHRT was likely to enhance scores in the 505 agility test, and possibly improve predicted peak speed when compared with training in normoxia. However, improvements in the sport-specific tests were greater following BFR training than IHRT. It is possible that due to the relatively high occlusive pressures used (up to 230 mmHg), the BFR condition caused lower levels of muscle oxygenation than the IHRT group, enhancing training adaptations. However, as muscle oxygenation status was not monitored by Manimmanakorn et al. [29], it is difficult to explain these results based on muscle hypoxia alone. It is also possible that cellular swelling was increased via occluded venous outflow in the BFR group, triggering an anabolic signalling cascade not replicated in the IHRT group [12]. Further research examining the mechanisms underlying hypertrophic responses to IHRT is warranted before these changes can be comprehensively described.

3.1.3 Perceptual Responses

Currently, little data have described the perceptual responses to IHRT. Nishimura et al. [17] and Kon et al. [16] reported no significant differences in RPE and subjective fatigue, respectively, between groups completing resistance exercise in hypoxia and normoxia. In contrast, Manimmanakorn et al. [29] reported that subjective pain was significantly higher in subjects performing IHRT than those in the control or BFR groups. Previous research has noted pain increases in direct correlation with H^+ concentration during tourniquet ischaemia [122]. However, if the increased pain reported by Manimmanakorn et al. [29] was associated with additional metabolic stress, greater hypertrophic and strength improvements would also be expected from IHRT compared with the BFR group. It is therefore difficult to explain the mechanisms causing the differences in pain between the training conditions, based on current understanding, and further research is required before the perceptual responses to IHRT can be fully described.

3.2 Potential Mechanisms of IHRT for Hypertrophy and Strength

3.2.1 Concentration of Metabolites

The accumulation of metabolites is suggested to mediate, at least in part, many of the mechanisms that affect muscle hypertrophy [46]. Kon et al. [15] examined the metabolic responses to five sets of ten repetitions of bench press and leg press exercises (70 % 1RM) in systemic hypoxia ($F_IO_2 = 0.13$) and normoxia ($F_IO_2 = 0.21$) in active young men. Greater blood lactate responses were reported for the hypoxia group than the normoxia group (1.2-fold higher). Similar findings were reported by the same researchers using lower intensity exercise (5 sets of 14 repetitions at 50 % 1RM; $F_IO_2 = 0.13$) [16]. Thus, in agreement with BFR research, it appears that lactate accumulation is augmented following IHRT. To the authors' best knowledge, no other investigations have examined the concentration of metabolites following IHRT, and further research is required to quantify the metabolic responses to such exercise.

3.2.2 Hormonal Responses

To date, only two investigations have assessed the hormonal responses to resistance exercise in systemic hypoxia [15, 16]. Similar to BFR research, an augmented GH response occurs following low- [16] and moderate-intensity [15] resistance exercise in systemic hypoxia. However, while serum IGF-1 increased immediately following resistance exercise in both hypoxia and normoxia, there were no significant differences between conditions [15]. This is in agreement with previous BFR research, where GH response is typically augmented following resistance exercise with BFR, while the IGF-1 response appears equivocal [51, 55]. Similarly, whilst serum testosterone levels were significantly increased following resistance exercise in both hypoxia and normoxia, no

significant differences were found between conditions [15, 16]. These findings are also in agreement with BFR research, and might reflect dissociation between the magnitude of metabolic stress and testosterone responses [5, 63].

Kon et al. [15] reported significantly larger increases in epinephrine (1.5-fold) and norepinephrine (1.2-fold) following moderate-intensity resistance exercise in hypoxia than in normoxia, as well as significant increases in cortisol (1.5-fold) only in the hypoxia group. These factors suggest that a hypoxic stimulus may increase the physiological and/or psychological stress, potentially causing a catabolic effect [57]. However, contrasting results were reported by Kon et al. [16], who observed no significant differences in plasma norepinephrine or cortisol levels after low-intensity resistance exercise in either hypoxia or normoxia. This disagreement may be explained by differences in the intensity of resistance exercise, as catecholamine and cortisol responses typically reflect the acute demands of exercise, and may be dependent upon the force of muscle contractions [5, 57, 69]. Nonetheless, as previously described in Sect. 2.2.2, it is important to note that the role of systemic endocrine responses in muscular hypertrophy is currently a point of debate among scientists. Further research regarding the mechanisms by which hormones can augment hypertrophic responses is necessary before this potential mechanism can be elucidated.

3.2.3 Intramuscular Signalling Pathways

Previous research has demonstrated that chronic exposure to hypoxia adversely affects protein kinase B/mTOR signalling [123], upregulates myostatin expression [124], and subsequently leads to atrophy in skeletal muscle [125]. However, the response of intramuscular signalling pathways to acute hypoxic exposure during resistance exercise remains unclear. Etheridge et al. [126] reported that following moderate-intensity IHRT (6 sets of 8 repetitions at 70 % 1RM; 3.5 h exposure to $F_IO_2 = 0.12$), MPS was blunted, despite an increase in S6K1 phosphorylation. These results are somewhat disparate with BFR research, where increases in S6K1 phosphorylation have been reported in congruence with increases in MPS [51, 77]. While speculative, Etheridge et al. [126] propose that other currently unknown signalling processes might override mTOR signalling in hypoxia, affecting the physiological responses to resistance exercise in hypoxia [126]. Additionally, the suppression of MPS following resistance exercise in hypoxia was correlated with the magnitude of decreases in arterial oxygen saturation ($r^2 = 0.49$; $p < 0.05$). This indicates that subjects who exhibited a lesser degree of hypoxaemia had a greater capacity to maintain post-exercise MPS. However, while the results of Etheridge et al. [126] indicate that resistance exercise in acute systemic hypoxia may elicit a diminished MPS response, it is important to recognize that the duration of hypoxic exposure (3.5 h) in this study was longer than typical IHRT research [15–17]. When considering the atrophying effects of chronic hypoxia on skeletal muscle [125], it may be that exposure for as little as 3.5 h can mitigate the potentially anabolic effects of IHRT.

Hypoxia is known to activate hypoxia inducible factor (HIF)-1α, which acts as the primary transcriptional response factor for hypoxic adaptation [127]. In turn, HIF-1α stimulates expression of vascular endothelial growth factor (VEGF) [128], which promotes angiogenesis [18]. While expression of HIF-1α and VEGF might have benefits in bone remodelling and repair [129, 130], the role of this pathway in hypertrophy is not yet understood [53]. Arsic et al. [130] reported that VEGF could stimulate skeletal muscle fibre regeneration and growth in vivo; however, this research utilised an animal model, and the effects of VEGF on hypertrophy in human subjects is less clear, and warrants research attention.

A novel factor that might contribute to intracellular signalling is whether hypobaric or normobaric hypoxia is employed during exercise. Research indicates that hypobaric hypoxia (e.g. terrestrial altitude) causes a decrease in plasma nitric oxide concentration, whereas normobaric hypoxia (e.g. via nitrogen dilution hypoxic generators) does not [131]. Nitric oxide is a potent reactive species and has been proposed to mediate the activation of skeletal muscle satellite cells and subsequent hypertrophy [132]. It is therefore possible that the type of hypoxia employed during IHRT may influence the subsequent physiological responses. However, no research has yet compared the responses to resistance exercise under hypobaric and normobaric hypoxia.

Skeletal muscle responses to hypoxic resistance exercise might also be affected by an upregulation of autophagy-lysosomal pathways during periods of metabolic or hypoxic stress [133]. The autophagy-lysosomal pathway contributes largely to catabolic processes in atrophying muscle [134]. While the signalling pathways by which autophagic processes occur in skeletal muscle are complex (for a comprehensive review see Schiaffino et al. [135]), it appears that mTOR complex 1 can promote both protein synthesis and autophagy. Indeed, despite the proteolytic effects of autophagic processes, it appears that they are crucial to the maintenance of muscle mass [133]. When considering the totality of research, the effects of hypoxia on both anabolic and catabolic signalling pathways remain largely unknown [136]. Further research is therefore required before a comprehensive understanding of the how hypoxic exposure can affect intramuscular signalling pathways can be reached.

3.2.4 Skeletal Muscle Function

While skeletal muscle function and activation has been extensively researched using BFR techniques, only Manimmanakorn et al. [121] have reported on the responses of skeletal muscle to resistance exercise in systemic hypoxia. Electrical activity of the knee extensors was assessed during tests of muscular strength and endurance in netball athletes prior to, and following, 5 weeks of low-intensity resistance training with either BFR, systemic hypoxia, or no additional stimulus (i.e. control). While all groups demonstrated significantly greater muscle activation during strength and endurance tasks following training, the largest increases were reported in the BFR group [121]. This may suggest that the neuromuscular changes were most influenced by the restriction of blood flow, rather than hypoxia per se. Nonetheless, it is also possible that oxygen delivery to the muscles in the IHRT group could have been maintained by increased peripheral blood flow, despite a reduced arterial oxygen saturation, thus limiting the hypoxic stimulus experienced by the muscles [121]. Previous research has also demonstrated that breathing hypoxic air during cycle ergometer exercise increases recruitment of type II muscle fibres compared with normoxia [137]. It is therefore plausible to hypothesize that, similarly to BFR exercise, systemic hypoxia could stimulate an increased type II motor unit recruitment. Although the level of intramuscular hypoxia created, and the resultant muscle activation, may be of a lesser magnitude during exercise with systemic hypoxia than with BFR. Further research is required to fully elucidate how breathing hypoxic air during resistance exercise can alter the oxygenation status of skeletal muscle, and influence subsequent motor unit recruitment.

4 Differences Between BFR and IHRT Methods

While the adaptation to resistance training with BFR or IHRT may be largely mediated by the hypoxia stimulus, it is important to note how these specific methods may differ. Perhaps the most pertinent of these differences is the haemodynamic response, which is facilitated during BFR via the application of external pressure to limb vasculature, and via systemic hypoxia during IHRT. Indeed, ischaemia/reperfusion and hypoxia/reoxygenation have resulted in different genetic responses in an animal model [138]. Reductions in blood flow via BFR result in lower muscle oxygenation levels during resistance exercise, and greater reperfusion following exercise, than observed during high-intensity exercise without BFR [18]. As such, it would be expected that a greater reactive hyperaemic response would follow BFR than IHRT, which may potentially mediate greater cellular swelling and anabolic signalling [12]. However, it should be recognized that recent evidence does not support an anabolic role of reactive hyperaemia in MPS following BFR resistance exercise [102]. These findings might reflect a decreased delivery of nutrients, growth factors and hormones to the limb during BFR (which is not experienced during IHRT), although the role of systemic responses in hypertrophy has also been questioned [71, 72].

Exercising in hypoxia is known to trigger a compensatory vasodilation to match an increased oxygen demand at the muscular level [139]. As mechanical pressure is not applied to the vasculature during IHRT, this compensatory vasodilation might attenuate decreased tissue oxygenation, thus reducing the localised hypoxic stimulus in working muscle. Furthermore, it is likely that type II muscle fibres may be more sensitive to increased perfusion (i.e. via hypoxia-induced vasodilation) than type I fibres [140], owing to their greater fractional oxygen extraction if highly perfused [141]. This increased microvascular oxygen delivery may cause type II fibres to behave more like their oxidatively efficient type I counterparts [142], potentially attenuating contractile fatigue. Also, as severe hypoxia has been demonstrated to alter function of the central nervous system [143], the possibility exists that systemic hypoxia may affect motor unit recruitment, although this is yet to be clarified in IHRT research. Taken together, these data suggest that IHRT might be fibre-type selective, having most effect on type II fibres. While this hypothesis remains speculative, it is possible that IHRT is optimised by higher intensities than typically used during BFR training due to its potential impact on type II fibres.

The practical implications of the two hypoxic resistance training strategies discussed may differ greatly. We propose that BFR resistance training is most useful for individuals who are unable to train at moderate- or high-intensity (e.g. the elderly, rehabilitation patients or athletes seeking to manage total training load), yet may still benefit from increases in muscular strength and size. Separately, IHRT may be of more benefit for athletic populations, as multi-joint exercises can be performed under hypoxic conditions, and there is the potential to train at a much higher intensity under increased neurological demand.

5 Conclusions

In the past decade, research has established that low-intensity resistance training with BFR can facilitate greater muscular gains than equivalent training without BFR. We propose that this is influenced by the anabolic environment resulting from localized hypoxia during BFR, although the exact

mechanisms at play remain unclear. It is likely that these adaptations are dependent on a multitude of factors, including mechanical stress, neuromotor control, metabolic demands, endocrine activities, cellular swelling and intramuscular signalling [8, 12, 15]. Recently, research has suggested that IHRT elicits similar responses, while offering several practical benefits over BFR methods, particularly for athletic populations. However, few investigations have examined this technique, and as such it is difficult to make recommendations for implementing IHRT based on current understanding. It should also be acknowledged that a number of mechanisms proposed to facilitate the augmented responses to both BFR training and IHRT remain poorly understood, particularly the systemic role of hormonal responses and cellular swelling. Future research should examine the physiological, performance and perceptual responses to resistance exercise and training in systemic hypoxia, as well as the mechanisms underpinning adaptation to both BFR resistance exercise and IHRT.

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References

1. Kraemer WJ, Fleck SJ, Evans WJ. Strength and power training: physiological mechanisms of adaptation. Exerc Sport Sci Rev. 1996;24:363–97.
2. Bird SP, Tarpenning KM, Marino FE. Designing resistance training programmes to enhance muscular fitness: a review of the acute programme variables. Sports Med. 2005;35(10):841–51.
3. Spiering BA, Kraemer WJ, Anderson JM, et al. Resistance exercise biology: manipulation of resistance exercise programme variables determines the responses of cellular and molecular signalling pathways. Sports Med. 2008;38(7):527–40.
4. Gordon SE, Kraemer WJ, Vos NH, et al. Effect of acid–base balance on the growth hormone response to acute high-intensity cycle exercise. J Appl Physiol. 1994;76(2):821–9.
5. Goto K, Ishii N, Kizuka T, et al. The impact of metabolic stress on hormonal responses and muscular adaptations. Med Sci Sports Exerc. 2005;37(6):955–63.
6. Hakkinen K, Pakarinen A, Alen M, et al. Neuromuscular and hormonal adaptations in athletes to strength training in two years. J Appl Physiol. 1988;65(6):2406–12.
7. Viru M, Jansson E, Viru A, et al. Effect of restricted blood flow on exercise-induced hormone changes in healthy men. Eur J Appl Physiol Occup Physiol. 1998;77(6):517–22.
8. Takarada Y, Nakamura Y, Aruga S, et al. Rapid increase in plasma growth hormone after low-intensity resistance exercise with vascular occlusion. J Appl Physiol. 2000;88(1):61–5.
9. Florini JR, Ewton DZ, Coolican SA. Growth hormone and the insulin-like growth factor system in myogenesis. Endocr Rev. 1996;17(5):481–517.
10. McCall GE, Byrnes WC, Fleck SJ, et al. Acute and chronic hormonal responses to resistance training designed to promote muscle hypertrophy. Can J Appl Physiol. 1999;24(1):96–107.
11. Crewther B, Keogh J, Cronin J, et al. Possible stimuli for strength and power adaptation: acute hormonal responses. Sports Med. 2006;36(3):215–38.
12. Loenneke JP, Fahs CA, Rossow LM, et al. The anabolic benefits of venous blood flow restriction training may be induced by muscle cell swelling. Med Hypotheses. 2012;78(1):151–4.
13. Takarada Y, Takazawa H, Sato Y, et al. Effects of resistance exercise combined with moderate vascular occlusion on muscular function in humans. J Appl Physiol. 2000;88(6):2097–106.
14. Shinohara M, Kouzaki M, Yoshihisa T, et al. Efficacy of tourniquet ischemia for strength training with low resistance. Eur J Appl Physiol Occup Physiol. 1998;77(1–2):189–91.
15. Kon M, Ikeda T, Homma T, et al. Effects of acute hypoxia on metabolic and hormonal responses to resistance exercise. Med Sci Sports Exerc. 2010;42(7):1279–785.
16. Kon M, Ikeda T, Homma T, et al. Effects of low-intensity resistance exercise under acute systemic hypoxia on hormonal responses. J Strength Cond Res. 2012;26(3):611–7.
17. Nishimura A, Sugita M, Kato K, et al. Hypoxia increases muscle hypertrophy induced by resistance training. Int J Sports Physiol Perform. 2010;5(4):497–508.
18. Takano H, Morita T, Iida H, et al. Hemodynamic and hormonal responses to a short-term low-intensity resistance exercise with the reduction of muscle blood flow. Eur J Appl Physiol. 2005;95(1):65–73.
19. Loenneke JP, Kearney ML, Thrower AD, et al. The acute response of practical occlusion in the knee extensors. J Strength Cond Res. 2010;24(10):2831–4.
20. Loenneke JP, Pujol TJ. The use of occlusion training to produce muscle hypertrophy. Strength Cond J. 2009;31(3):77–84.
21. Sumide T, Sakuraba K, Sawaki K, et al. Effect of resistance exercise training combined with relatively low vascular occlusion. J Sci Med Sport. 2009;12(1):107–12.
22. Nakajima T, Morita T, Sato Y. Key considerations when conducting KAATSU training. Int J KAATSU Training Res. 2011;7(1):1–6.
23. ACSM. American College of Sports Medicine position stand: progression models in resistance training for healthy adults. Med Sci Sports Exerc. 2009;41(3):687–708.
24. Abe T, Yasuda T, Midorikawa T, et al. Skeletal muscle size and circulating IGF-1 are increased after two weeks of twice daily KAATSU resistance training. Int J KAATSU Training Res. 2005;1(1):6–12.
25. Takarada Y, Sato Y, Ishii N. Effects of resistance exercise combined with vascular occlusion on muscle function in athletes. Eur J Appl Physiol. 2002;86(4):308–14.
26. Takarada Y, Tsuruta T, Ishii N. Cooperative effects of exercise and occlusive stimuli on muscular function in low-intensity resistance exercise with moderate vascular occlusion. Jpn J Physiol. 2004;54(6):585–92.
27. Madarame H, Neya M, Ochi E, et al. Cross-transfer effects of resistance training with blood flow restriction. Med Sci Sports Exerc. 2008;40(2):258–63.
28. Kacin A, Strazar K. Frequent low-load ischemic resistance exercise to failure enhances muscle oxygen delivery and endurance capacity. Scand J Med Sci Sports. 2011;21(6):e231–41.
29. Manimmanakorn A, Hamlin MJ, Ross JJ, et al. 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. 2013;16(4):337–42.
30. Abe T, Kawamoto K, Yasuda T, et al. Eight days KAATSU-resistance training improved sprint but not jump performance in collegiate male track and field athletes. Int J KAATSU Training Res. 2005;1(1):19–23.

31. Yamanaka T, Farley RS, Caputo JL. Occlusion training increases muscular strength in division IA football players. J Strength Cond Res. 2012;26(9):2523–9.
32. Cook CJ, Kilduff LP, Beaven CM. Three weeks of occlusion training can improve strength and power in trained athletes. Int J Sports Physiol Perform. 2014;9(1):166–72.
33. Schantz P, Randall-Fox E, Hutchison W, et al. Muscle fibre type distribution, muscle cross-sectional area and maximal voluntary strength in humans. Acta Physiol Scand. 1983;117(2):219–26.
34. Yasuda T, Fujita T, Miyagi Y, et al. Electromyographic responses of arm and chest muscle during bench press exercise with and without KAATSU. Int J KAATSU Training Res. 2006;2(1):15–8.
35. Yasuda T, Brechue WF, Fujita T, et al. Muscle activation during low-intensity muscle contractions with restricted blood flow. J Sports Sci. 2009;27(5):479–89.
36. Moore DR, Burgomaster KA, Schofield LM, et al. Neuromuscular adaptations in human muscle following low intensity resistance training with vascular occlusion. Eur J Appl Physiol. 2004;92(4–5):399–406.
37. Gabriel DA, Kamen G, Frost G. Neural adaptations to resistive exercise: mechanisms and recommendations for training practices. Sports Med. 2006;36(2):133–49.
38. Behm DG. Neuromuscular implications and applications of resistance training. J Strength Cond Res. 1995;9(4):264–74.
39. Cook SB, Murphy BG, Labarbera KE. Neuromuscular function after a bout of low-load blood flow-restricted exercise. Med Sci Sports Exerc. 2013;45(1):67–74.
40. Manini TM, Clark BC. Blood flow restricted exercise and skeletal muscle health. Exerc Sport Sci Rev. 2009;37(2):78–85.
41. Wernbom M, Jarrebring R, Andreasson MA, et al. Acute effects of blood flow restriction on muscle activity and endurance during fatiguing dynamic knee extensions at low load. J Strength Cond Res. 2009;23(8):2389–95.
42. Wernbom M, Augustsson J, Thomee R. Effects of vascular occlusion on muscular endurance in dynamic knee extension exercise at different submaximal loads. J Strength Cond Res. 2006;20(2):372–7.
43. Loenneke JP, Balapur A, Thrower AD, et al. The perceptual responses to occluded exercise. Int J Sports Med. 2011;32(3):181–4.
44. Graham B, Breault MJ, McEwen JA, et al. Occlusion of arterial flow in the extremities at subsystolic pressures through the use of wide tourniquet cuffs. Clin Orthop Relat Res. 1993;286:257–61.
45. Crenshaw AG, Hargens AR, Gershuni DH, et al. Wide tourniquet cuffs more effective at lower inflation pressures. Acta Orthop Scand. 1988;59(4):447–51.
46. Schoenfeld BJ. Potential mechanisms for a role of metabolic stress in hypertrophic adaptations to resistance training. Sports Med. 2013;43(3):179–94.
47. Suga T, Okita K, Takada S, et al. Effect of multiple set on intramuscular metabolic stress during low-intensity resistance exercise with blood flow restriction. Eur J Appl Physiol. 2012;112(11):3915–20.
48. Suga T, Okita K, Morita N, et al. Intramuscular metabolism during low-intensity resistance exercise with blood flow restriction. J Appl Physiol. 2009;106(4):1119–24.
49. Takada S, Okita K, Suga T, et al. Low-intensity exercise can increase muscle mass and strength proportionally to enhanced metabolic stress under ischemic conditions. J Appl Physiol. 2012;113(2):199–205.
50. Reeves GV, Kraemer RR, Hollander DB, et al. Comparison of hormone responses following light resistance exercise with partial vascular occlusion and moderately difficult resistance exercise without occlusion. J Appl Physiol. 2006;101(6):1616–22.
51. Fujita S, Abe T, Drummond MJ, et al. Blood flow restriction during low-intensity resistance exercise increases S6K1 phosphorylation and muscle protein synthesis. J Appl Physiol. 2007;103(3):903–10.
52. Pierce JR, Clark BC, Ploutz-Snyder LL, et al. Growth hormone and muscle function responses to skeletal muscle ischemia. J Appl Physiol. 2006;101(6):1588–95.
53. Kawada S. What phenomena do occur in blood flow-restricted muscle? Int J KAATSU Training Res. 2005;1(2):37–44.
54. Schoenfeld BJ. The mechanisms of muscle hypertrophy and their application to resistance training. J Strength Cond Res. 2010;24(10):2857–72.
55. Patterson SD, Leggate M, Nimmo MA, et al. Circulating hormone and cytokine response to low-load resistance training with blood flow restriction in older men. Eur J Appl Physiol. 2013;113(3):713–9.
56. Kraemer RR, Kilgore JL, Kraemer GR, et al. Growth hormone, IGF-I, and testosterone responses to resistive exercise. Med Sci Sports Exerc. 1992;24(12):1346–52.
57. Kraemer WJ, Ratamess NA. Hormonal responses and adaptations to resistance exercise and training. Sports Med. 2005;35(4):339–61.
58. Le Roith D, Bondy C, Yakar S, et al. The somatomedin hypothesis: 2001. Endocr Rev. 2001;22(1):53–74.
59. Borst SE, De Hoyos DV, Garzarella L, et al. Effects of resistance training on insulin-like growth factor-1 and IGF binding proteins. Med Sci Sports Exerc. 2001;33(4):648–53.
60. Marx JO, Ratamess NA, Nindl BC, et al. Low-volume circuit versus high-volume periodized resistance training in women. Med Sci Sports Exerc. 2001;33(4):635–43.
61. Chandler RM, Byrne HK, Patterson JG, et al. Dietary supplements affect the anabolic hormones after weight-training exercise. J Appl Physiol. 1994;76(2):839–45.
62. Kraemer WJ, Marchitelli L, Gordon SE, et al. Hormonal and growth factor responses to heavy resistance exercise protocols. J Appl Physiol. 1990;69(4):1442–50.
63. Durand RJ, Castracane VD, Hollander DB, et al. Hormonal responses from concentric and eccentric muscle contractions. Med Sci Sports Exerc. 2003;35(6):937–43.
64. Pope ZK, Willardson JM, Schoenfeld BJ. Exercise and blood flow restriction. J Strength Cond Res. 2013;27(10):2914–26.
65. Kraemer WJ. Neuroendocrine responses to resistance exercise. In: Baechle TR, editor. Essentials of straining training and conditioning. Champaign: Human Kinetics; 2000. p. 91–114.
66. Giustina A, Veldhuis JD. Pathophysiology of the neuroregulation of growth hormone secretion in experimental animals and the human. Endocr Rev. 1998;19(6):717–97.
67. Weltman A, Pritzlaff CJ, Wideman L, et al. Exercise-dependent growth hormone release is linked to markers of heightened central adrenergic outflow. J Appl Physiol. 2000;89(2):629–35.
68. Godfrey RJ, Madgwick Z, Whyte GP. The exercise-induced growth hormone response in athletes. Sports Med. 2003;33(8):599–613.
69. Smilios I, Pilianidis T, Karamouzis M, et al. Hormonal responses after various resistance exercise protocols. Med Sci Sports Exerc. 2003;35(4):644–54.
70. Kraemer WJ, Fleck SJ, Callister R, et al. Training responses of plasma beta-endorphin, adrenocorticotropin, and cortisol. Med Sci Sports Exerc. 1989;21(2):146–53.
71. West DW, Phillips SM. Anabolic processes in human skeletal muscle: restoring the identities of growth hormone and testosterone. Phys Sportsmed. 2010;38(3):97–104.

72. West DW, Burd NA, Staples AW, et al. Human exercise-mediated skeletal muscle hypertrophy is an intrinsic process. Int J Biochem Cell Biol. 2010;42(9):1371–5.
73. Nielsen JL, Aagaard P, Bech RD, et al. Proliferation of myogenic stem cells in human skeletal muscle in response to low-load resistance training with blood flow restriction. J Physiol. 2012;590(Pt 17):4351–61.
74. Hornberger TA, Stuppard R, Conley KE, et al. Mechanical stimuli regulate rapamycin-sensitive signalling by a phosphoinositide 3-kinase-, protein kinase B- and growth factor-independent mechanism. Biochem J. 2004;380(Pt 3):795–804.
75. Wang X, Proud CG. The mTOR pathway in the control of protein synthesis. Physiology (Bethesda). 2006;21:362–9.
76. Bodine SC, Stitt TN, Gonzalez M, et al. Akt/mTOR pathway is a crucial regulator of skeletal muscle hypertrophy and can prevent muscle atrophy in vivo. Nat Cell Biol. 2001;3(11):1014–9.
77. Fry CS, Glynn EL, Drummond MJ, et al. Blood flow restriction exercise stimulates mTORC1 signaling and muscle protein synthesis in older men. J Appl Physiol. 2010;108(5):1199–209.
78. Wernbom M, Apro W, Paulsen G, et al. Acute low-load resistance exercise with and without blood flow restriction increased protein signalling and number of satellite cells in human skeletal muscle. Eur J Appl Physiol. 2013;113(12):2953–65.
79. Wernbom M, Augustsson J, Raastad T. Ischemic strength training: a low-load alternative to heavy resistance exercise? Scand J Med Sci Sports. 2008;18(4):401–16.
80. Thannickal VJ, Fanburg BL. Reactive oxygen species in cell signaling. Am J Physiol Lung Cell Mol Physiol. 2000;279(6):L1005–28.
81. Valko M, Leibfritz D, Moncol J, et al. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol. 2007;39(1):44–84.
82. Suzuki YJ, Ford GD. Redox regulation of signal transduction in cardiac and smooth muscle. J Mol Cell Cardiol. 1999;31(2):345–53.
83. Tamaki T, Uchiyama S, Tamura T, et al. Changes in muscle oxygenation during weight-lifting exercise. Eur J Appl Physiol. 1994;68(6):465–9.
84. Korthuis RJ, Granger DN, Townsley MI, et al. The role of oxygen-derived free radicals in ischemia-induced increases in canine skeletal muscle vascular permeability. Circ Res. 1985;57(4):599–609.
85. Goldfarb AH, Garten RS, Chee PD, et al. Resistance exercise effects on blood glutathione status and plasma protein carbonyls: influence of partial vascular occlusion. Eur J Appl Physiol. 2008;104(5):813–9.
86. Roth SM, Walsh S. Myostatin: a therapeutic target for skeletal muscle wasting. Curr Opin Clin Nutr Metab Care. 2004;7(3):259–63.
87. Roth SM, Martel GF, Ferrell RE, et al. Myostatin gene expression is reduced in humans with heavy-resistance strength training: a brief communication. Exp Biol Med (Maywood). 2003;228(6):706–9.
88. Kim JS, Cross JM, Bamman MM. Impact of resistance loading on myostatin expression and cell cycle regulation in young and older men and women. Am J Physiol Endocrinol Metab. 2005;288(6):E1110–9.
89. Hulmi JJ, Ahtiainen JP, Kaasalainen T, et al. Postexercise myostatin and activin IIb mRNA levels: effects of strength training. Med Sci Sports Exerc. 2007;39(2):289–97.
90. Petrella JK, Kim JS, Cross JM, et al. Efficacy of myonuclear addition may explain differential myofiber growth among resistance-trained young and older men and women. Am J Physiol Endocrinol Metab. 2006;291(5):E937–46.
91. Walker KS, Kambadur R, Sharma M, et al. Resistance training alters plasma myostatin but not IGF-1 in healthy men. Med Sci Sports Exerc. 2004;36(5):787–93.
92. Drummond MJ, Fujita S, Abe T, et al. Human muscle gene expression following resistance exercise and blood flow restriction. Med Sci Sports Exerc. 2008;40(4):691–8.
93. Laurentino GC, Ugrinowitsch C, Roschel H, et al. Strength training with blood flow restriction diminishes myostatin gene expression. Med Sci Sports Exerc. 2012;44(3):406–12.
94. Kawada S, Ishii N. Skeletal muscle hypertrophy after chronic restriction of venous blood flow in rats. Med Sci Sports Exerc. 2005;37(7):1144–450.
95. Manini TM, Vincent KR, Leeuwenburgh CL, et al. Myogenic and proteolytic mRNA expression following blood flow restricted exercise. Acta Physiol (Oxf). 2011;201(2):255–63.
96. Abe T, Loenneke JP, Fahs CA, et al. Exercise intensity and muscle hypertrophy in blood flow-restricted limbs and non-restricted muscles: a brief review. Clin Physiol Funct Imaging. 2012;32(4):247–52.
97. Fujita T, Brechue W, Kurita K, et al. Increased muscle volume and strength following six days of low-intensity resistance training with restricted muscle blood flow. Int J KAATSU Training Res. 2008;4(1):1–8.
98. Sjogaard G, Adams RP, Saltin B. Water and ion shifts in skeletal muscle of humans with intense dynamic knee extension. Am J Physiol Regul Integr Comp Physiol. 1985;248(2 Pt 2):R190–6.
99. Lang F, Busch GL, Ritter M, et al. Functional significance of cell volume regulatory mechanisms. Physiol Rev. 1998;78(1):247–306.
100. Dangott B, Schultz E, Mozdziak PE. Dietary creatine monohydrate supplementation increases satellite cell mitotic activity during compensatory hypertrophy. Int J Sports Med. 2000;21(1):13–6.
101. Lang F. Mechanisms and significance of cell volume regulation. J Am Coll Nutr. 2007;26(Suppl 5):613S–23S.
102. Gundermann DM, Fry CS, Dickinson JM, et al. Reactive hyperemia is not responsible for stimulating muscle protein synthesis following blood flow restriction exercise. J Appl Physiol. 2012;112(9):1520–8.
103. Moritani T, Sherman WM, Shibata M, et al. Oxygen availability and motor unit activity in humans. Eur J Appl Physiol Occup Physiol. 1992;64(6):552–6.
104. Sundberg CJ. Exercise and training during graded leg ischaemia in healthy man with special reference to effects on skeletal muscle. Acta Physiol Scand Suppl. 1994;615:1–50.
105. Henneman E, Somjen G, Carpenter DO. Functional significance of cell size in spinal motoneurons. J Neurophysiol. 1965;28:560–80.
106. Loenneke JP, Fahs CA, Wilson JM, et al. Blood flow restriction: the metabolite/volume threshold theory. Med Hypotheses. 2011;77(5):748–52.
107. Yasuda T, Abe T, Brechue WF, et al. Venous blood gas and metabolite response to low-intensity muscle contractions with external limb compression. Metabolism. 2010;59(10):1510–9.
108. Rotto DM, Kaufman MP. Effect of metabolic products of muscular contraction on discharge of group III and IV afferents. J Appl Physiol. 1988;64(6):2306–13.
109. Leonard CT, Kane J, Perdaems J, et al. Neural modulation of muscle contractile properties during fatigue: afferent feedback dependence. Electroencephalogr Clin Neurophysiol. 1994;93(3):209–17.
110. Abe T. Effects of short-term low-intensity KAATSU training on strength and skeletal muscle size in young men [in Japanese with English abstract]. J Train Sci Exerc Sports. 2004;16:199–207.
111. Yasuda T, Fujita S, Ogasawara R, et al. Effects of low-intensity bench press training with restricted arm muscle blood flow on chest muscle hypertrophy: a pilot study. Clin Physiol Funct Imaging. 2010;30(5):338–43.

112. Yasuda T, Ogasawara R, Sakamaki M, et al. Relationship between limb and trunk muscle hypertrophy following high-intensity resistance training and blood flow-restricted low-intensity resistance training. Clin Physiol Funct Imaging. 2011;31(5):347–51.
113. Meeuwsen T, Hendriksen IJ, Holewijn M. Training-induced increases in sea-level performance are enhanced by acute intermittent hypobaric hypoxia. Eur J Appl Physiol. 2001;84(4):283–90.
114. Bonetti DL, Hopkins WG, Kilding AE. High-intensity kayak performance after adaptation to intermittent hypoxia. Int J Sports Physiol Perform. 2006;1(3):246–60.
115. Vogt M, Puntschart A, Geiser J, et al. Molecular adaptations in human skeletal muscle to endurance training under simulated hypoxic conditions. J Appl Physiol. 2001;91(1):173–82.
116. Roels B, Thomas C, Bentley DJ, et al. Effects of intermittent hypoxic training on amino and fatty acid oxidative combustion in human permeabilized muscle fibers. J Appl Physiol. 2007;102(1):79–86.
117. Lundby C, Calbet JA, Robach P. The response of human skeletal muscle tissue to hypoxia. Cell Mol Life Sci. 2009;66(22):3615–23.
118. Millet GP, Roels B, Schmitt L, et al. Combining hypoxic methods for peak performance. Sports Med. 2010;40(1):1–25.
119. Pesta D, Hoppel F, Macek C, et al. Similar qualitative and quantitative changes of mitochondrial respiration following strength and endurance training in normoxia and hypoxia in sedentary humans. Am J Physiol Regul Integr Comp Physiol. 2011;301(4):R1078–87.
120. Friedmann B, Kinscherf R, Borisch S, et al. Effects of low-resistance/high-repetition strength training in hypoxia on muscle structure and gene expression. Pflügers Arch Eur J Physiol. 2003;446(6):742–51.
121. Manimmanakorn A, Manimmanakorn N, Taylor R, et al. Effects of resistance training combined with vascular occlusion or hypoxia on neuromuscular function in athletes. Eur J Appl Physiol. 2013;113(7):1767–74.
122. Issberner U, Reeh PW, Steen KH. Pain due to tissue acidosis: a mechanism for inflammatory and ischemic myalgia? Neurosci Lett. 1996;208(3):191–4.
123. Favier FB, Costes F, Defour A, et al. Downregulation of Akt/mammalian target of rapamycin pathway in skeletal muscle is associated with increased REDD1 expression in response to chronic hypoxia. Am J Physiol Regul Integr Comp Physiol. 2010;298(6):R1659–66.
124. Hayot M, Rodriguez J, Vernus B, et al. Myostatin up-regulation is associated with the skeletal muscle response to hypoxic stimuli. Mol Cell Endocrinol. 2011;332(1–2):38–47.
125. MacDougall JD, Green HJ, Sutton JR, et al. Operation Everest II: structural adaptations in skeletal muscle in response to extreme simulated altitude. Acta Physiol Scand. 1991;142(3):421–7.
126. 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 J Physiol Endocrinol Metab. 2011;301(4):697–702.
127. Mason S, Johnson RS. The role of HIF-1 in hypoxic response in the skeletal muscle. Adv Exp Med Biol. 2007;618:229–44.
128. Semenza GL. Regulation of oxygen homeostasis by hypoxia-inducible factor 1. Physiology (Bethesda). 2009;24:97–106.
129. Loenneke JP, Young KC, Fahs CA, et al. Blood flow restriction: rationale for improving bone. Med Hypotheses. 2012;78(4):523–7.
130. Arsic N, Zacchigna S, Zentilin L, et al. Vascular endothelial growth factor stimulates skeletal muscle regeneration in vivo. Mol Ther. 2004;10(5):844–54.
131. Faiss R, Pialoux V, Sartori C, et al. Ventilation, oxidative stress, and nitric oxide in hypobaric versus normobaric hypoxia. Med Sci Sports Exerc. 2013;45(2):253–60.
132. Anderson JE. A role for nitric oxide in muscle repair: nitric oxide-mediated activation of muscle satellite cells. Mol Biol Cell. 2000;11(5):1859–74.
133. Masiero E, Agatea L, Mammucari C, et al. Autophagy is required to maintain muscle mass. Cell Metab. 2009;10(6):507–15.
134. Sandri M. Autophagy in skeletal muscle. FEBS Lett. 2010;584(7):1411–6.
135. Schiaffino S, Dyar KA, Ciciliot S, et al. Mechanisms regulating skeletal muscle growth and atrophy. FEBS J. 2013;280(17):4294–314.
136. Bigard X. Molecular factors involved in the control of muscle mass during hypoxia-exposure: the main hypotheses are revisited. Acta Physiol (Oxf). 2013;208(3):222–3.
137. Melissa L, MacDougall JD, Tarnopolsky MA, et al. Skeletal muscle adaptations to training under normobaric hypoxic versus normoxic conditions. Med Sci Sports Exerc. 1997;29(2):238–43.
138. Aravindan N, Williams MT, Riedel BJ, et al. Transcriptional responses of rat skeletal muscle following hypoxia-reoxygenation and near ischaemia-reperfusion. Acta Physiol Scand. 2005;183(4):367–77.
139. Casey DP, Joyner MJ. Compensatory vasodilatation during hypoxic exercise: mechanisms responsible for matching oxygen supply to demand. J Physiol. 2012;590(24):6321–6.
140. Faiss R, Girard O, Millet GP. Advancing hypoxic training in team sports: from intermittent hypoxic training to repeated sprint training in hypoxia. Br J Sports Med. 2013;47(Suppl 1):i45–50.
141. McDonough P, Behnke BJ, Padilla DJ, et al. Control of microvascular oxygen pressures in rat muscles comprised of different fibre types. J Physiol. 2005;563(Pt 3):903–13.
142. Cleland SM, Murias JM, Kowalchuk JM, et al. Effects of prior heavy-intensity exercise on oxygen uptake and muscle deoxygenation kinetics of a subsequent heavy-intensity cycling and knee-extension exercise. Appl Physiol Nutr Metab. 2012;37(1):138–48.
143. Downing SE, Mitchell JH, Wallace AG. Cardiovascular responses to ischemia, hypoxia, and hypercapnia of the central nervous system. Am J Physiol Leg Cont. 1963;204(5):881–7.