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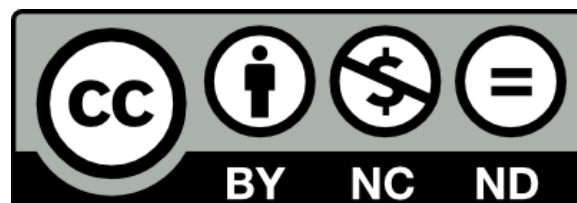
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Title: Intermittent hypoxic resistance training: is metabolic stress the key moderator?

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ABSTRACT

Traditionally, researchers and practitioners have manipulated acute resistance exercise variables to elicit the desired responses to training. However, recent research indicates that altering the muscular environment during resistance training, namely by implementing a hypoxic stimulus, can augment muscle hypertrophy and strength. Intermittent hypoxic resistance training (IHRT), whereby participants inspire hypoxic air during resistance training, has been previously demonstrated to increase muscle cross-sectional area and maximum strength by significantly greater amounts than the equivalent training in normoxia. However, some recent evidence has provided conflicting results, reporting that the use of systemic hypoxia during resistance training provided no added benefit. While the definitive mechanisms that may augment muscular responses to IHRT are not yet fully understood, an increased metabolic stress is thought to be important for moderating many downstream processes related to hypertrophy. It is likely that methodological differences between conflicting IHRT studies have resulted in different degrees of metabolic stress during training, particularly when considering the inter-set recovery intervals used. Given that the most fundamental physiological stresses resulting from hypoxia are disturbances to oxidative metabolism, it becomes apparent that resistance training may only benefit from additional hypoxia if the exercise is structured to elicit a strong metabolic response. We hypothesize that for IHRT to be more effective in producing muscular hypertrophy and increasing strength than the equivalent normoxic training, exercise should be performed with relatively brief inter-set recovery periods, with the aim of providing a potent metabolic stimulus to enhance anabolic responses.

INTRODUCTION

Resistance exercise is known to have a potent affect on skeletal muscle morphology and functional adaptations. Traditionally, researchers and practitioners have focused on manipulating acute resistance exercise variables to elicit the desired training response. These variables include the muscle action, loading and volume, exercise selection and order, inter-set rest periods, repetition velocity and training frequency [1]. However, recent evidence suggests that methods to alter the intramuscular environment during resistance exercise can be beneficial for stimulating hypertrophy and increases in muscular strength. The use of blood flow restriction (BFR) during resistance training has become increasingly popular for this purpose. This technique involves the application of a restrictive cuff, tourniquet or elastic wraps around the top of a limb, with the aim to somewhat maintain arterial inflow while occluding venous return from the exercising limb [2].

This technique creates a localized hypoxic environment in the limb during exercise, which is proposed to impact on downstream mechanisms that promote muscular development [3]. The novel aspect of training with BFR is that substantial improvements in muscular hypertrophy and strength are possible even when using low-loads (20-40% of concentric 1-repetition maximum [1RM]) for both clinical [4] and athletic [5,6] populations. However, while the muscles of the trunk may benefit to some degree from BFR exercise [7], the trunk muscles are unable to be trained under the same conditions as the limbs. Furthermore, due to the low-loads employed during BFR exercise, motor unit recruitment (as estimated by surface electromyography) is lower than during traditional high-load exercise [8,9], therefore limiting the potential for neuromuscular adaptations.

Another method to manipulate the intramuscular environment during resistance exercise that is not affected by these limitations is the addition of systemic hypoxia during training. Research has demonstrated that hypertrophic and strength responses can be enhanced by breathing hypoxic air during low-load (20% 1RM) [6,10] and moderate-load (70% 1RM) [11] resistance training. However, some more recent evidence has provided conflicting results, reporting no additional benefit for muscular development following resistance training in systemic hypoxia [12,13]. While scientific understanding of intermittent hypoxic resistance training (IHRT) is in its infancy, it appears that these conflicting results may be a result of differences in the research methodologies employed.

In particular, the inter-set rest periods used by researchers has varied greatly (30-120 s). Inter-set rest periods are often overlooked in the design of resistance training programs, particularly in recreational training settings. However, the rest period is a primary determinant of the overall intensity of a training session, particularly when the level of available oxygen is altered as it will directly impact on the metabolic stress induced by exercise [14]. As the metabolic response to resistance exercise is a proposed key moderator of subsequent adaptive responses [15], it stands to reason that inter-set rest periods should be carefully programmed during IHRT. In this paper, we hypothesize that due to the disturbances in energetic metabolism induced by hypoxia, the inter-set rest periods employed during IHRT are of primary importance to enhanced hypertrophic responses.

CONFLICTING RESULTS OF IHRT STUDIES

To date, six separate investigations have assessed the efficacy of IHRT for increased muscle hypertrophy and strength, compared with the equivalent training in

normoxia. These studies are summarized in Table 1. Two papers have used low-load resistance training (20-30% 1RM), with Manimmanakorn et al. [6,10] employing very brief inter-set rest periods (30 s), while Friedmann, et al. [16] used longer rest intervals (60 s). Interestingly, Manimmanakorn et al. [6,10] reported that IHRT elicited greater hypertrophic and strength responses than work-matched normoxic training, whereas Friedmann, et al. [16] observed no changes in strength or muscle cross-sectional area (mCSA) after either IHRT or normoxic training, though muscular endurance increased in both groups.

Similar findings have been reported for IHRT research using moderate-loads (70% 1RM or 10RM). Two investigations that employed comparable training protocols with 60 s inter-set recovery periods have demonstrated significantly enhanced hypertrophic responses for IHRT groups compared to work-matched normoxic training groups [11,17]. However, other investigations using similar training loads but with extended inter-set recovery intervals (90-120 s) have demonstrated no added benefit for training under hypoxia [12,13]. Although it is too early to make definitive recommendations based on only these investigations, we hypothesize that low- and moderate-load IHRT might only provide added benefit when relatively brief inter-set rest periods are used. Indeed, when considering the fundamental physiological stress that hypoxia adds to resistance training (disturbances to oxidative metabolism), it is likely that a threshold for inter-set rest duration exists, and that the use of longer recovery periods between sets might mitigate any hypoxia-mediated effects on the muscular environment.

INSERT TABLE 1 NEAR HERE

EFFECTS OF INTER-SET REST PERIODS ON ENERGETIC METABOLISM

Inter-set rest periods are most often manipulated in response to the intensity of exercise being performed. For example, maximal strength and power training (1-6 repetitions per set using heavy loads) generally utilize long rest intervals (180-480 s) to allow for sufficient neuromuscular recovery, and replenishment of adenosine triphosphate (ATP) and phosphocreatine (PCr) stores [14,18]. However, training focused on hypertrophic responses (8-12 repetitions per set using moderate loads) employs relatively short rest periods (60-120 s) in order to increase intramuscular metabolic stress [1], at the expense of contractile function in subsequent sets [19]. This form of training is fuelled primarily by energy from the ATP-PCr system, with minor contributions from oxidative metabolism [14]. Muscular endurance training (>15 repetitions per set using light loads) utilizes brief rest intervals (30-45 s), with an increased reliance on aerobic metabolism.

The inter-set rest period not only determines how much of the ATP-PCr energy source is able to be recovered between sets, but also the degree to which metabolic products (e.g. lactate and hydrogen ions) are removed from the exercising musculature prior to the next set. Metabolic stress is proposed as an important moderator of hypertrophy following resistance training [15]. As such, it appears that resistance training programs that use relatively short inter-set rest periods provide a greater stimulus for hypertrophy than those using longer rest periods. This can be observed anecdotally by comparing the moderate-load training with brief rest periods typically employed by bodybuilders, to the high-load training with long rest periods used by powerlifters. While powerlifters are generally much stronger (largely due to

greater neuromuscular development), bodybuilders exhibit a greater degree of muscle hypertrophy, owing to the differences in training structure between these groups.

HYPOXIA-MEDIATED CHALLENGES FOR ENERGETIC METABOLISM

The importance of oxygen availability for PCr resynthesis was first established by Harris, et al. [20], who implemented a pneumatic cuff around the thigh (240 mmHg) for 6 minutes following a bout of isometric knee extension. As a result of the ischemic condition, PCr resynthesis was completely suppressed. Furthermore, when the cuff was deflated for 25 s following 90 s of ischemic recovery and then reinflated, PCr stores recovered to levels that would be expected following 25 s of free flow recovery. Similar findings have also been presented using a systemic hypoxia model, with Haseler, et al. [21] reporting that the PCr recovery rates following plantar flexion exercise were slower when participants breathed hypoxic air (fraction of inspired oxygen [$F_{I}O_2$] = 10%) compared to normoxic air ($F_{I}O_2$ = 21%), and that PCr recovery was fastest when breathing hyperoxic air ($F_{I}O_2$ = 100%). Taken together, these findings indicate that the availability of oxygen following an exercise bout is vital for PCr resynthesis, and perhaps more importantly, that the time course of PCr resynthesis kinetics can be altered through manipulating oxygen availability.

Decreased levels of available oxygen during IHRT may also alter energetic metabolism during each set, placing more reliance on anaerobic energy production. While no data have been presented to detail whether the contributions of different energy systems is altered by performing resistance exercise in hypoxia, research examining energy production during sustained running exercise has demonstrated that short duration performance can be maintained due to a shift toward anaerobic metabolism [22]. Participants performed maximal running efforts for durations

ranging from 15-180 s in normoxia and hypoxia ($F_{I}O_2 = 13\%$). Despite reductions in the oxidative energy available for sprinting under hypoxic conditions, participants were able to run just as fast for sprints of up to 60 s, and nearly as fast for sprints of up to 120 s. The authors concluded that this was possible because rates of anaerobic energy release (estimated from oxygen deficit) increased by as much as 18%, compensating for the reductions in aerobic power. Additionally, previous research has observed increased concentrations of blood lactate, which is well known as a by-product of anaerobic metabolism, following both low-load [23] and moderate-load [24] IHRT compared to the equivalent normoxic exercise. Taken together, these findings indicate that there is a shift towards anaerobic metabolism during IHRT. However, research from our laboratory has observed no significant difference in blood lactate concentrations following high-load resistance exercise with extended rest periods (180 s) in normoxia and two hypoxic conditions ($F_{I}O_2 = 16\%$ and 13% ; unpublished findings). This may indicate that protocols designed specifically to enhance muscular strength (i.e. high-load with sufficient inter-set recovery) do not benefit substantially by the addition of systemic hypoxia.

As repeated resistance exercise sets are largely dependent on the ATP-PCr energy system, it stands to reason that if the inter-set rest periods are manipulated so that PCr stores are not completely recovered, subsequent sets will be performed under more challenging metabolic conditions. However, if inter-set recovery periods during IHRT are too long, PCr stores may return to levels similar to normoxic resistance exercise between sets, mitigating any additive benefit from the hypoxic stimulus. This relationship has been previously illustrated in a review by Glaister [25], who interpreted the work of Haseler, et al. [21] to demonstrate that while PCr levels may be lower at 60 s post exercise in hypoxia compared with normoxia, after 90-120 s of

recovery, there does not appear to be a difference between the conditions. However, these data are specific to submaximal plantar flexion exercise, and caution should be taken when considering these findings for IHRT. Figure 1 represents a hypothetical model of how hypoxia-related metabolic stress may be attenuated over time following a set of resistance exercise. These hypothetical relationships are likely to be affected by both the rate of recovery from metabolic stress (i.e. PCr resynthesis and removal of metabolites), as well as the degree of metabolic stress induced by the hypoxic condition and exercise stimulus.

INSERT FIGURE 1 NEAR HERE

ANABOLIC EFFECTS OF METABOLIC STRESS

The hypertrophic responses to resistance training are thought to be largely related to the metabolic stress induced by exercise, which is typically estimated via the accumulation of metabolites such as lactate, hydrogen ions and inorganic phosphate, and by changes in pH levels. Recently, it has been proposed that increased levels of metabolic stress can impact on several downstream mechanisms to facilitate muscular hypertrophy [3,15]. For example, it is possible that metabolic stress can increase the recruitment of muscle fibres. Under normal conditions, muscle fibre recruitment follows the size principle, which dictates that smaller motor units are recruited first, with the larger and more powerful motor units being recruited with increasing exercise loads [26]. However, given that metabolic acidosis can stimulate group III and IV afferents [27], mechanistically speaking, a reflexive net inhibitory effect on the α -motor neuron may result [28], facilitating increased fibre recruitment to protect against conduction failure [29]. Simply stated, if a greater number of

muscle fibres are stimulated during a training session, then a greater portion of the muscle must respond to the exercise stress and undergo adaptation.

Another potential role for metabolic stress in muscular hypertrophy is increased cellular swelling. Transient cellular swelling is a well known response to the resistance training protocols commonly performed by bodybuilders to elicit hypertrophy, and has been proposed as a mediator for adaptive muscular responses [30]. Loenneke, et al. [31] have recently hypothesized that the anabolic benefits of low-load resistance training with BFR may be induced by acute swelling of muscle cells. Cell swelling is maximized in exercise that relies on anaerobic metabolism, due to the osmotic changes caused by lactate accumulation [32]. Thus a resultant increase in the flow of water into the muscle cell is required to equilibrate the osmotic gradient [31]. Although it is likely that cellular swelling may be induced to a greater degree during BFR exercise than IHRT, due to the substantial venous pooling resulting from occluded venous return under BFR conditions, an accumulation of metabolites during IHRT [23,24] may increase cellular swelling alone. Given that hydration-mediated cellular swelling can increase protein synthesis and decrease protein degradation in hepatocytes [33] and a range of other cells [34], it is possible that similar responses occur in muscle cells. Muscle cell swelling may be detected by an intrinsic volume sensor [31], that registers a threat to cellular integrity causing the cell to initiate a signalling response to reinforce its ultrastructure [15,35]. Although a paucity of research has directly examined the downstream signalling events following exercise-mediated muscle cell swelling, it is suggested that mammalian target of rapamycin and mitogen-activated protein kinase pathways may be activated [15,31,35], which are known to be important for muscle hypertrophy.

Metabolic stress is also often proposed as a mechanism by which growth-orientated hormone concentrations can be increased [15]. Theoretically, higher concentrations of hormones increase the likelihood of receptor interactions [36], thereby enhancing the action of these hormones. In particular, increased growth hormone concentrations have been reported following low-load [23] and moderate-load [13,24] IHRT. Post-exercise elevations in growth hormone may be mediated by increased lactate and/or hydrogen ion build-up [37]. Furthermore, reduced pH levels associated with metabolic acidosis may potentiate release of growth hormone via chemoreflex stimulation mediated by intramuscular metaboreceptors and group III and IV afferents [38,39]. However, while growth hormone has often been cited as having important anabolic functions for skeletal muscle, the role of acute exercise-induced endocrine responses in muscle hypertrophy has been recently questioned, and may not have anabolic effects in healthy individuals as once thought [40]. Therefore, further research is required to clarify this, and other potential mechanisms for hypertrophy resulting from resistance training.

CONSIDERATIONS FOR TRAINING PROGRAMS

From current evidence, it appears that relatively short inter-set rest periods are required during IHRT to take advantage of hypoxia-mediated disturbances to oxidative metabolism, and subsequently enhance hypertrophic responses. Furthermore, it is likely that, as with traditional resistance training, the inter-set rest period is related to the intensity of the loads lifted. Low-load IHRT appears beneficial when using very brief rest periods (30 s), whereas moderate-load IHRT is most effective when using slightly longer (60 s) rest periods. However, if the inter-set recovery interval is extended past these durations, the hypoxia-mediated alterations in

energy system contributions and subsequent metabolic stress are likely to be attenuated. This is highlighted by recent research from Ho, et al. [12] and Kon, et al. [13], who used relatively long inter-set rest periods (120 and 90 s, respectively) and observed no added benefit for hypertrophic or strength responses following IHRT compared to the equivalent training in normoxia. We believe that while investigations using longer rest periods are necessary to broaden scientific understanding of IHRT methods, it is premature to conclude that the addition of hypoxia to resistance training does not provide added muscular benefit based on the results of research using longer inter-set rest periods.

In order to test the hypotheses presented in this paper, future research should aim to assess whether resistance training programs with varying inter-set rest intervals result in different morphological changes when performed in hypoxia. Furthermore, it is possible that some resistance training methods that have been developed to increase the degree of metabolic stress (e.g. drop sets and assisted-repetition sets) may provide the best responses when used during IHRT. It is also likely that if appropriate inter-set rest periods are used during IHRT, the metabolic stress will continue to accumulate with each new set, effectively beginning each set at a higher level of metabolic stress. Therefore, we propose that multiple sets using the same muscle groups would exaggerate the intramuscular metabolic stress, and indeed a number of sets may be required to observe large differences in hypertrophic responses between IHRT and the equivalent training in normoxia. Further research to determine the optimal resistance training methods to use in combination with systemic hypoxia is therefore warranted.

However, it is important to highlight that exaggerated metabolic stress resulting from IHRT could adversely affect exercise performance during the each training session. If this is the case, caution should be taken not to use IHRT as a sole

method of muscular development. Additional research is warranted to assess the impact of systemic hypoxia on resistance training performance, particularly when exercise is structured to facilitate a potent metabolic response. Furthermore, as the mechanisms underpinning adaptive responses to IHRT are not yet fully understood, it is possible that factors not related to metabolic stress (e.g. increased production of reactive oxygen species) may play a role in muscular development following this form of training [3]. Although it is likely that metabolic stress plays an important role in hypertrophic responses, it would be remiss not to recognize that skeletal muscle adaptations are vastly complex, and most probably affected by numerous physiological processes.

CONCLUSIONS

In conclusion, it is important when designing IHRT research studies that we consider the fundamental physiological stressors imposed by hypoxia (disturbances to oxidative metabolic processes). We hypothesize that the added benefits for muscular growth and strength will only be facilitated by IHRT programs that make use of short inter-set rest periods, with the aim to enhance the metabolic responses to exercise. More specifically, it appears that low-load IHRT requires rest intervals of ~30 s, whereas moderate-load IHRT should employ intervals of ~60 s. Future studies aiming to assess the potential hypertrophic and strength benefits of IHRT should implement a resistance training program that induce a marked degree of metabolic stress, as this is both a likely variable to be affected by hypoxia, and is proposed to act as a moderator for downstream process that can enhance hypertrophy and strength. In addition, future research should examine whether IHRT can evoke more substantial muscular gains than volume-equated traditional resistance training methods.

CONFLICT OF INTEREST STATEMENT

None of the authors report any conflicts of interest.

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FIGURE CAPTIONS

Fig. 1. Theoretical time-course changes of intramuscular metabolic stress following a set of moderate-load traditional resistance exercise, moderate-load IHRT and low-load BFR exercise (BFR maintained following exercise). We propose that inter-set rest periods during IHRT should be structured to take advantage of hypoxia-mediated metabolic stress (30-60 s in this hypothetical example).

Note: As it is not common to employ continuous BFR for greater than 60 s between sets, this hypothetical response has not been illustrated for the same duration as other responses.

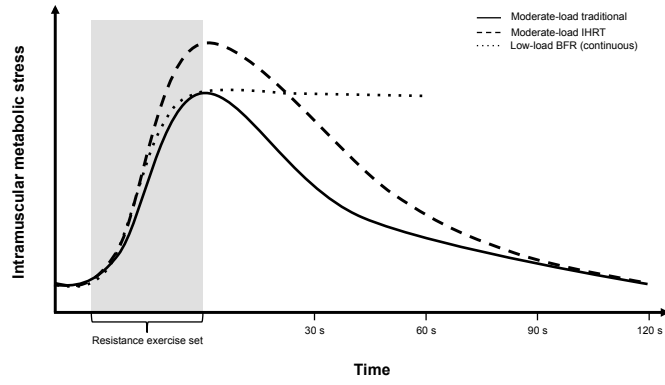
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Table 1. Summary of research examining the morphological and strength responses to IHRT programs.

Study	Training conditions	Exercise (intensity)	Sets x reps (inter-set rest)	Training frequency/duration	Hypertrophic and strength responses	Hypoxia beneficial?
Low-load IHRT ($\leq 30\%$ 1RM)						
Manimmanakorn et al. [6] and [10]	<ul style="list-style-type: none"> IHRT (SpO₂ at ~80%) RT (ambient air) 	Knee extension and flexion (20% 1RM)	3 x ~22-36 (30 s)	3 days/week (5 weeks)	<ul style="list-style-type: none"> Greater ↑ muscular strength and endurance after IHRT Greater ↑ in mCSA after IHRT 	Yes
Friedmann et al. [16]	<ul style="list-style-type: none"> IHRT (F_IO₂ = 12%) RT (ambient air) 	Knee extension (30% 1RM)	6 x 25 (60 s)	3 days/week (4 weeks)	<ul style="list-style-type: none"> ↔ Isokinetic strength and mCSA, ↑ Muscular endurance (not different between groups) 	No
Moderate-load IHRT (70% 1RM or 10RM)						
Nishimura et al. [11]	<ul style="list-style-type: none"> IHRT (F_IO₂ = 16%) RT (F_IO₂ = 21%) 	Elbow extension and flexion (70% 1RM)	4 x 10 (60 s)	2 days/week (6 weeks)	<ul style="list-style-type: none"> ↑ mCSA only after IHRT ↑ 1RM after just 3 weeks for IHRT 	Yes
Kurobe et al. [17]	<ul style="list-style-type: none"> IHRT (F_IO₂ = 12.7%) RT (F_IO₂ = 21%) 	Elbow extension (10RM)	3 x 10 (60 s)	3 days/week (8 weeks)	<ul style="list-style-type: none"> Greater ↑ muscle thickness after IHRT ↑ 10RM (not different between groups) 	Yes
Kon et al. [13]	<ul style="list-style-type: none"> IHRT (F_IO₂ = 14.4%) RT (F_IO₂ = 21%) 	Bench press and leg press (70% 1RM)	5 x 10 (90 s)	2 days/week (8 weeks)	<ul style="list-style-type: none"> ↑ 1RM strength (not different between groups) ↑ mCSA (not different between groups) 	No
Ho et al. [12]	<ul style="list-style-type: none"> IHRT (F_IO₂ = 15%) RT (F_IO₂ = 21%) 	Squat (10RM)	3 x 10 (120 s)	3 days/week (6 weeks)	<ul style="list-style-type: none"> ↑ Squat 1RM (not different between groups) ↔ Body composition in either group 	No

reps repetitions, IHRT intermittent hypoxic resistance training, SpO₂ arterial oxygen saturation, RT resistance training in normoxia, F_IO₂ fraction of inspired oxygen, 1RM 1-repetition maximum, mCSA muscle cross sectional area, 10RM 10-repetition maximum] increase, ↔ no significant change.

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