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Physiological stimuli necessary for muscle hypertrophy

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Abstract This paper reviews the existing literature about muscle hypertrophy resulting from various types of training to document the significance of mechanical and metabolic stresses, and to challenge the conventional ideas of achieving hypertrophy that exclusively rely on highload resistance training. Low-load resistance training can induce comparable hypertrophy to that of high-load resistance training when each bout or set is performed until lifting failure. This is attributable to the greater exercise volume and metabolic stress achieved with low-load exercise at lifting failure, which, however, results in a prolonged exercise bout. Endurance exercises (walking and cycling) at moderate intensity are also capable of eliciting muscle hypertrophy, but at much slower rates (months rather than weeks) in limited muscle or age groups. Blood flow restriction (BFR) in working muscles, however, accelerates the development of metabolic fatigue, alleviating the time consuming issue associated with low-load or endurance training. These alternative training methods, however, cannot completely replace conventional high-load resistance training, which provides superior strength gain as well as performance improvement even for trained individuals. The alternative approaches, therefore, may be considered for those who are less enthusiastic or under certain medical conditions, or who have limited or no access to proper equipment. However, people should be aware that low-load resistance training or endurance training entails substantial effort and/or discomfort at lifting failure or with BFR. Understanding the advantages and disadvantages of each method will help in assigning the most suitable training program for each client's goals and needs.

Keywords : training, metabolic stress, mechanical stress, lifting failure, blood flow restriction

Introduction

Training under high external load or high mechanical stress, has been advocated in order to maximize muscle hypertrophy¹). However, recent research has shown that, when each exercise set is performed until volitional failure, low-load resistance exercise can induce comparable hypertrophy to that of high-load resistance exercise at the whole muscle or myofiber level^{2,3}). At lifting failure, the degree of fatigue or metabolic stress may be greater for low-load exercise, given that one cannot continue lifting repetitions even with light weights. The greater metabolic stress incurred by low-load exercise may compensate for the smaller mechanical stress, allowing the resultant physiological stimuli to be sufficient for morphological

adaptations. Moreover, numerous peer-reviewed papers over the past decade have indicated that the hypertrophic effect is augmented when low-load exercise training (i.e. 10-30% of maximum strength) is combined with blood flow restriction (BFR) in the working muscles^{4,5)}. These studies further corroborate the critical role of metabolic stress in muscle hypertrophy⁶⁾.

Additionally, endurance exercise (cycling or walking) at moderate intensity, that is designed particularly for general fitness - incurring much lower mechanical and metabolic stresses than that of resistance training - has been shown to increase muscle size when performed regularly for prolonged periods (i.e. over months rather than weeks)^{7,8}). This denotes that training quantity or duration, in addition to the degree of mechanical or metabolic stress per session, is a required physiological manipulation for muscle hypertrophy.

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The purposes of this paper are to review the existing literature related to muscle hypertrophy resulting from various types of exercise training, to explore the mechanisms underlying muscle hypertrophy, particularly the essential roles of mechanical and metabolic stresses, and to challenge the conventional approach to hypertrophy that relies exclusively on high-load resistance training.

Exercise load and muscle hypertrophy in resistance training

Skeletal muscle hypertrophy results from a prolonged shift of muscle protein turn-over towards synthesis rather than breakdown⁹⁾. Muscle protein synthesis can be enhanced by exercise stimuli through the following mechanisms: 1) exposure to exercise stimuli increasing the phosphorylation of the mechanistic target of rapamycin (mTOR), 2) increase in phosphorylation of the downstream targets of mTOR, i.e. eukaryotic translation initiation factor 4E binding protein 1 (4E-BP1) and ribosomal protein S6 kinase 1(S6K1), and 3) enhancement of mRNA translation (creation of proteins)¹⁰⁻¹⁵⁾. Numerous attempts have been made to uncover ideal training conditions for muscle hypertrophy.

Kumar et al. (2009) investigated the acute responses to resistance exercise at 20-90% of one repetition maximum (1RM) to compare the magnitudes of change in muscle protein synthesis and anabolic cell signaling (S6K1 and 4E-BP1 phosphorylation) between various resistance exercise loads in both young and older men¹⁶. The exercise was conducted as follows: 27 reps \times 3 sets at 20% 1RM, 14 reps \times 3 sets at 40%, 9 reps \times 3 sets at 60%, 8 reps \times 3 sets at 75%, or 3 reps \times 6 sets at 90%, so that the total work outputs were roughly equalized between exercise loads. Results showed that the post-exercise myofibrillar protein synthesis and phosphorylation levels of S6K1 and 4E-BP1 were greater for higher exercise loads up to 60% 1RM, with no further increase, however, occurring beyond 60% 1RM for both young and older adults. These results suggest that an exercise load of more than 60% 1RM is a requirement to maximize muscle protein synthesis and activation of cell signaling, assenting to the conventional approach (high mechanical stresses) for muscle hypertrophy¹). The authors, however, did not state whether the subjects reached lifting failure at each exercise load. Based on the relationship between training load and the number of repetitions available to date 17 , lifting failure may have been achieved for the higher exercise load groups; however, it was unlikely the case for the lower exercise loads, perhaps due to the equalization of total work output with respect to that attained with the highest exercise load. This poses a question as to whether levels of muscle protein synthesis and cell signaling activation following the low load exercise would have been greater than observed if repetitions were continued until failure.

As an answer to the question, Burd et al. (2010) conducted a study comparing muscle protein synthesis and anabolic signaling after 4 sets of unilateral leg extension between 3 conditions: 1) 90% 1RM until failure in each set, 2) 30% 1RM until failure in each set, 3) 30% 1RM with work output matched with that of condition 1 in each set¹³). When the amount of work was equalized (condition 1 vs. 3), the rate of myofibrillar protein synthesis at 4 h post-30% 1RM exercise was about one half of that observed following the 90% 1RM exercise, agreeing with the results of Kumer et al.¹⁶. However, when performed until volitional failure (condition 1 vs. 2), the rate of protein synthesis was similar between the 90% 1RM and 30% 1RM conditions. Notably, the elevated synthetic rate was sustained longer for the 30% 1RM to failure condition than the 90% 1RM condition. Furthermore, an increase in S6K1 phosphorylation at 4 h post-exercise was observed only for the 30% 1RM to failure condition. These greater physiological responses after exercising at 30% 1RM may be ascribed to a substantially greater work performed than the 90% 1RM condition when each exercise set was continued until true failure. This suggests that the muscular hypertrophic responses may be mediated not only by external load, but also by exercise volume.

The importance of exercise volume or lifting failure to augment the hypertrophic effect may be further supported in the context of metabolic stress⁶. Metabolic stress results from the accumulation of metabolic by-products such as H⁺ and Pi¹⁸. It has been hypothesized that the development of metabolic stress triggers secondary reactions including the recruitment of additional motor units to compensate for the force loss¹⁹⁾, elevation of systemic hormones²⁰⁾, greater acute muscle cell swelling²¹⁾ and production of reactive oxygen species $(ROS)^{22}$. These mechanisms may increase the rate of muscle protein synthesis through activation of anabolic and/or prevention of catabolic signaling pathways, leading to hypertrophy²³⁻²⁶⁾ as well as the proliferation of satellite cells²⁷⁾. The fact that low load exercise imposes greater metabolic stress has been demonstrated by a previous EMG study²⁸⁾. The median power frequency of working muscles (bench press at 40, 50, 60, 70 or 80% 1RM) after repetition failure was greater for lower exercise loads, which incurred greater numbers of repetitions and longer exercise durations, than higher loads. A greater metabolic stress with low load exercise was further supported by reasoning that lifting at 40% 1RM might allow an approximate 60% fall in maximum force output; whereas lifting at 80% 1RM would allow only a 20% fall before unsuccessful lifting. And, a 60% fall in maximal force output must reflect a greater level of fatigue than only $20\%^{28}$.

The prospect of eliciting muscle hypertrophy with low load resistance training, however, needs to be confirmed by means of training studies and measurements of muscle mass or cross sectional area (CSA) since the studies above examined the acute changes of signal pathways only. Campos et al. (2002) investigated the effect of resistance training programs using various intensities on muscle size; and their results have been cited in many articles stating that high external loading is required for muscle hypertrophy²⁹⁾. In the study, subjects were divided into the following three groups: a low repetition group (4 sets \times 3-5 RM), an intermediate repetition group (3 sets \times 9-11 RM) and a high repetition group (2 sets \times 20-28 RM). Training volume (resistance \times repetitions \times sets) was, however, equalized between the groups. After an 8-week training period, hypertrophic effects were observed for the low and intermediate repetition groups, whereas no significant increase in muscle size occurred for the high repetition group. As described earlier, a low load exercise results in greater total work despite a smaller external load due to more repetitions performed within an exercise set. In this study, the number of sets was, however, reduced for higher repetition groups to control training volume, which may have eliminated the advantage of low load training; although each set was continued until failure.

A study by Mitchell et al. (2012) investigated the effects of low- and high-load training on muscle hypertrophy, using the following 3 groups: 3 sets \times 30% 1RM to failure, 3 sets \times 80% 1RM to failure, and 1 set \times 80% 1RM to failure²⁾. The changes in muscle size and strength were evaluated after a 10-week training, consisting of 3 sessions per week. As a result, the magnitude of muscle hypertrophy was similar between the 3 sets \times 30% 1RM and the 3 sets \times 80% 1RM groups, but 1 set \times 80% 1RM resulted in the smallest increase in muscle size. Furthermore, a more recent study has shown that a single set of 20% 1RM to failure resulted in comparable muscle hypertrophy to that of 2 sets of 80% 1RM (total work output was greater for 1 set \times 20% 1RM) in older adults³⁰. These results were in agreement with the aforementioned studies of signal pathways, suggesting the importance of total exercise volume and metabolic stress for muscle hypertrophy. However, it should be noted that strength gain (1RM strength) was greater for the higher exercise loads in these studies^{2,30}, implying that low-load exercise cannot completely replace high-load exercise. Importantly, these studies were conducted on untrained or recreationally active adults, with the training period being less than 3 months. It remains to be investigated whether the hypertrophic effect of low-load resistance exercise would hold for trained individuals or for longer training periods.

Muscle hypertrophy with endurance training

Endurance training is widely recommended as a major exercise modality to improve aerobic capacity and cardiovascular health. Given the significant role of exercise volume in hypertrophy based on resistance training research, it may be possible that even endurance training, which incurs much less mechanical stress than resistance training, can induce muscle hypertrophy if the volume of work reaches the threshold. In fact, some studies have demonstrated significant muscle hypertrophy after endurance training such as cycling or walking^{7,8,31,32)}. In this section, we discuss the potential of cycling and walking exercises for inducing muscle hypertrophy.

Hypertrophic effect of cycling. Professional cyclists have larger thigh muscles (at the whole muscle and myofiber levels) compared to normal individuals³³⁻³⁵⁾. The greater muscle size may be accounted for by their race specific training, other training such as high power pedaling, resistance training, genetic factors, or a combination of them. It is, therefore, difficult to differentiate the sole effect of cycling on muscle size from these confounding factors by referring to reports of cross sectional comparisons. Instead, the results of training studies employing untrained subjects ought to be reviewed.

Firstly, Nelson et al. (1990) observed muscle hypertrophy after a cycle training program (for 30-60 min at 75-85% HRmax per session) that was undertaken 4 days per week for 20 weeks³⁶⁾. A more recent study by Harber et al. (2012) showed that quadriceps muscle volume significantly increased by 5-6% after 12 weeks of cycle training (3-4 days per week at 60-80% HR reserve) in both untrained or minimally-trained young and older men³⁷⁾. A study by Bell et al. (2000), however, showed no muscle hypertrophy after 12 weeks of cycle training performed at progressively increasing intensity with sessions (initially at the ventilatory threshold up to 90% VO₂max) for 21-42 min per day, 3 days per week³¹⁾. This discrepancy could be due to the total number of sessions constituting the training program, which was less for the study of Bell et al. (i.e., 36 sessions) than Nelson et al. (80 sessions) or Harber et al. (42 sessions). We reported that, for untrained subjects, muscle hypertrophy was more likely to take place when the total number of cycle training sessions exceeded 40 times, and this trend was consistent between young and older adults⁸⁾. Resistance training, however, requires fewer sessions until significant muscle hypertrophy is observed (e.g., 18 sessions or 6 weeks)³⁸⁾. This implies that cycling training is capable of eliciting muscle hypertrophy, but at slower rates, due to smaller mechanical stresses imposed than resistance training.

To better understand the difference in hypertrophic rate between resistance training and cycling, we calculated the effect size (ES) of muscle hypertrophy using the following formula: ([post-test mean – pre-test mean] / pretest standard deviation [SD]). The ES was calculated for the results of two previous studies by Bell et al. (2000) and McCarthy et al. (2002), each of which evaluated the change of muscle size following both resistance and cycle training programs^{31,39}. The ES of lower body resistance training vs. continuous cycling was respectively 0.57 vs. 0.37 (3 times a week for 12 weeks) for Bell et al., and 1.15 vs. 0.17 (3 times a week for 10 weeks) for McCarthy et al. Obviously, the hypertrophic rate of cycle exercise is smaller than that of resistance training for a given training period.

One of the physiological mechanisms underlying muscle hypertrophy may involve the increased fluid pressure in the intracellular environment. Muscle contractions result in a change in the pressure gradient shifting the flow of plasma into the muscle fibers and/or interstitial spaces in exchange for accumulated metabolites^{6,40)}. Compared to other endurance exercises such as running, cycling may be more metabolically taxing because of longer contraction durations and less effective muscle pump (reduced chance of arterial preload)⁴¹⁾. Moreover, cycling is more energy consuming than running due to the lack of landing impact and thus minimal utilization of tendon elasticity⁴². These characteristics may increase the fluid diffusion to counter and restore the exacerbated intracellular environment. Importantly, cell swelling has been shown to trigger protein synthesis through the activation of mTOR and mitogen-activated protein kinase (MAPK)⁴⁰. Previous studies confirmed that a bout of continuous cycling (30-60 min at 40-75% VO₂max) was effective in temporarily increasing thigh thickness (swelling) (unpublished data), activating both the mTOR433 and MAPK443 signaling pathways, and increasing muscle protein synthesis⁴⁵⁾. Hence the contribution of intracellular fluid pressure and cellular swelling may explain muscle hypertrophy that results from cycle exercise.

The activation of mTOR signaling pathways, however, appears to be small or brief after cycle exercise compared to resistance exercise. For example, S6K1 phosphorylation has been shown to increase above basal levels immediately after both cycle and resistance exercise⁴⁶; but, after 4 h, the elevation of S6K1 phosphorylation remained only after the resistance exercise⁴⁶. Furthermore, one study showed that myofibrillar protein synthesis was stimulated over the 4 h period following resistance exercise, but not after cycle exercise⁴⁶. These demerits of cycling exercise, resulting from relatively small mechanical stresses, may account for the small effect size and many training sessions required for muscle hypertrophy compared to resistance training.

In addition to the protein synthesis, cycle exercise appears to affect the proteolytic system. A study by Harber et al. (2010) showed that Forkhead transcription factor 3A (FOXO3A), which is an indicator of proteolytic systems, significantly decreased 6 h after an acute bout of 60 min cycle exercise compared to rest⁴⁵). Furthermore, 12 weeks of cycle training, which induced muscle hypertrophy, significantly lowered the resting level of mRNA expression of FOXO3A^{47,48}. Therefore, the attenuation of protein breakdown may be another factor contributing to muscle hypertrophy following a cycling training program.

Hypertrophic effect of walking. In the last decade, there have been a limited number of studies that examined the relationship between accelerometer- (or pedometer-) de-

termined daily ambulatory activity and skeletal muscle size. In those studies, the data were collected from middle-aged and older populations (50 - 84 years old), with daily activities greater than 3 METs considered to be important for muscular adaptation^{49,50)}. Studies using dual energy X-ray absorptiometry (DXA), which estimates the lean tissue mass of the entire lower limb, however, produced mixed results as to the efficacy of daily ambulatory activity on muscle hypertrophy. Whereas, Abe et al. (2012) recently examined the correlation between the time spent for ambulatory activities at moderate - vigorous intensities (> 3 METs) and the muscle thickness using B-mode ultrasound, which allowed evaluation of individual lower limb muscle groups. They found a positive correlation between the time spent on moderate - vigorous ambulatory activities and muscle thickness for the tibialis anterior and triceps surae, suggesting that increased daily locomotor activities may prevent age-related loss of muscle mass in the lower leg muscles⁵¹⁾. However, a limitation of the study was that walking was not the only activity representing > 3 METs, and activities other than walking may have contributed to the reported relationship. To clarify the sole effect of walking on muscle size, the results of walk training studies employing untrained subjects are reviewed in the following section.

Studies concerning the influence of walk training on lower body muscle size have not been extensively conducted. However, some have shown that the thigh muscle size did not change after walk training performed 20 min/ day × 5 days/week × 6 weeks at 67 m/min, or 20 min/day \times 4 days/week \times 10 weeks at 75m/min in older adults^{52,53}. Whereas, Kubo et al. (2008) found that ultrasoundmeasured muscle thickness increased significantly for the knee flexors and dorsi flexors, no change occurred for the knee extensors or plantar flexors, following 6 months of walk training $(45.0 \pm 15.6 \text{ min/day} \times 5.4 \pm 1.1 \text{ days/week})$ at self-selected speed) in sedentary, or mild to moderately active older adults⁵⁴). Like cycle training, the discrepancy seems to be due to the length of the training program (6-10 weeks vs. 6 months), as well as training volume per day (20 min vs. 45 min) suggesting the possibility that beyond a certain quantitative threshold, walk training can also increase muscle size in older adults, albeit limited to specific muscle groups. The ES calculated for the study of Kubo et al. was 0.30, a similar value as the ES of cycle training in older adults (0.28), yet requiring a much longer period (6 months) than the cycle training (mean period = 14.8 weeks)⁸⁾. The hypertrophic effect of walk training is, therefore, lower than resistance training or cycle training. This finding is, however, reasonable given that the mechanical stress is much less for walking. According to an EMG study by Ericson et al. (1985), activation of the vastus lateralis and medialis during walking is less than one quarter of that during cycling⁵⁵⁾. Moreover, a bout of walk exercise failed to demonstrate the acute muscle swelling associated with cellular hydration to contend

with metabolic accumulation^{56,57)}. Hence, the involvement of the cell swelling due to fluid pressure may be reduced for walking.

To our knowledge, no studies have witnessed the hypertrophic effect when walk training alone is undertaken by young adults. One reason for the absence of the hypertrophic effect in young adults is that these studies employed overly short training periods (3 weeks)⁵⁸⁻⁶⁰⁾. A further explanation could be that young adults tend to be active and strong compared to older adults, so that walking does not turn out to be a sufficient exercise stimulus for hypertrophy. By contrast, for older adults with a reduced amount of daily activities, such a low exercise load from walking may still act as an effective stimulus to induce hypertrophy if carried out for a prolonged period. Furthermore, for body-mass bearing exercises, the exercise intensity depends on the ratio of lower body strength to body mass⁶¹. It is, therefore, possible that individuals with lower ratios (i.e., lower strength despite greater body mass) may benefit more from walk exercise in terms of muscle hypertrophy and strength gain.

Training with blood flow restriction (BFR)

In the earlier sections, we discussed the importance of metabolic stress for low-load resistance training to elicit muscle hypertrophy. To attain this, it was necessary to undergo each exercise set until lifting failure, which also leads to greater work performed. This strategy is remarkable, but time consuming. Similarly, we mentioned that endurance training such as cycling or walking was capable of inducing hypertrophy, but at much slower rates, requiring several weeks or months. To combat the temporal disadvantages, a new training strategy has been introduced. Blood flow restriction (BFR) accelerates the development of metabolic fatigue, and is considered an alternative method to increase training efficacy in the absence of high mechanical stress.

Hypertrophic effect of low-load resistance training combined with BFR. BFR in working muscles is achieved by wrapping a cuff around the proximal portion of a limb. Recently, Fahs et al. (2014) investigated the muscular adaptations of middle-aged men and women following a low-load resistance training program, consisting of 2 - 4 sets/day of unilateral knee extensions to failure × 3 days/ week \times 6 weeks (18 sessions) with one leg combined with BFR, and the other without BFR⁶²⁾. After the program, the thickness of the anterior quadriceps and strength increased for both limbs by similar degrees. The increase in lateral quadriceps thickness was, however, greater for the limb combined with BFR. Importantly, BFR produced less repetitions in each exercise set, hence the lower total exercise volume, due to a faster rate of metabolic fatigue⁶²⁾. This implies that metabolic stress, rather than exercise volume, is crucial in inducing muscular adaptations, and that BFR may alleviate the time consuming issue associated with low-load resistance training. These findings were supported by those of another study showing that the amount of acute muscle swelling following low-load resistance exercise performed to failure (indications of metabolic fatigue and resulting fluid pressure effect) was similar between the BFR and non-BFR conditions, although the exercise volume was reduced by BFR throughout the training session⁶³.

Hypertrophic effect of endurance training combined with BFR. By taking advantage of BFR, it is plausible that the hypertrophic effect of cycle or walk training can be augmented, and thus the program period required until significant hypertrophy occurs can be shortened. Abe et al. (2006) compared the effect of walking with and without BFR on muscle size and strength⁵⁹, in young men. The exercise consisted of 5 sets of 2 min walking (treadmill speed at 50 m/min), with 1 min rest between sets, which was undertaken twice a day, 6 days per week, for 3 weeks. The CSA of the thigh muscle and strength significantly increased only for the BFR group. Considering the conventional findings of the walking study, showing that older adults and about a 6-month period are requirements for observing hypertrophy, the findings of Abe et al. (2006) clearly demonstrated the potential of BFR. Not surprisingly, 6-10 weeks of walk training with BFR was effective in increasing muscle size for older adults^{52,53}.

The efficacy of BFR remains consistent for cycle training. After an 8-week training period with or without BFR (at 40% VO₂max for 15 min/day, 3 days/week, 24 sessions), the CSA and the volume of the thigh muscle increased for the BFR-cycle group only⁶⁴. In line with the studies of walking combined with BFR, BFR succeeded in shortening the training period required for cycle training to induce muscle hypertrophy (24 vs. 40 sessions).

To better elucidate the physiological role of BFR, we recently conducted a study comparing hypertrophyrelated cell signaling (i.e., mTOR and MAPK) between the BFR and the lower extremity and non-BFR (normal) conditions during walking⁶⁵⁾. We found that the phosphorylation of extracellular signal-related kinases (ERKs) 1/2 and p38, which promote the activation of MAPKinteracting kinases 1 and 2 (Mnk) 1 and Mnk2 (translation initiation)^{66,67}, were both elevated following BFR walking. Whereas, only the ERK 1/2 phosphorylation level was increased after normal walking. Furthermore, a lower phosphorylation of eEF2 (i.e., indicative of an accelerated translation elongation⁶⁸⁾) was observed for the BFR condition. The effects of BFR, however, may be greater for resistance training than for walking. In addition to the influences on ERK 1/2, p38 and eEF2, the phosphorylation of other selected proteins, particularly in the mTOR signaling pathway (i.e., mTOR, S6K1, S6) increased after a bout of low-load BFR resistance exercise^{23,69}. Moreover, the magnitude of change in phosphorylated cell signaling

after a low-load BFR resistance exercise was greater than that after a bout of BFR walking^{23,69)}. For instance, the ERK 1/2 phosphorylation level 3 h after a lower-leg BFR resistance exercise was approximately six times greater than the resting level, whereas it was only 4 times greater after BFR walking⁶⁹⁾. These results assent to existing findings that low-load BFR resistance exercise has produced greater muscle hypertrophy than that of BFR walking⁵⁾. Meta-analysis revealed that the mean ES of BFR walk training was 0.31 (6.8 times/week for 5.5 weeks), whereas it was 0.44 for low-load BFR resistance training (8.8 times/week for 3.6 weeks)⁵⁾, inferring a greater ES for BFR low-resistance training for a normalized period.

Implications

Based on the recent evidence, hypertrophic adaptations of the skeletal muscles result from exposure to both mechanical and metabolic stresses. Deriving a hypertrophic effect from relatively low-loaded training is plausible to some extent if the level of metabolic stress is increased by achieving lifting failure in each exercise set and/or by means of blood flow restriction. However, the exercise volume, the number of sessions or the training period required for a hypertrophic adaptation or strength gain may vary depending on the exercise modes. Trainers and therapists, therefore, may need to prescribe the most suitable training depending on the purposes of assigning exercise modalities, as well as the preferences of their clients (Table 1). Aiming for muscular adaptations using low-load exercise may be beneficial particularly to cardiovascular patients or patients in a post-surgery rehabilitation program, to whom high-load exercise may be contraindicated. Furthermore, endurance exercises such as walking and cycling, are familiar activities required in daily living, and thus may be recommended to individuals

Table 1. Various training modes suggested for muscular adaptations and their advantages and disadvantages

Training mode			Equipment	Trained muscles	Advantages	Disadvantages
Resistance training	High- load	Each set until failure	• Heavy weights	Whole body	 Maximizing strength gain Hypertrophy Effective for trained individuals 	 Risk of injury Unsafe for cardiovascular patients Requiring high enthusiasm
		Non-fatiguing set	• Light weights	Whole body	Skill acquisitionRehabilitation purposes	• Lack of evidence for MH
	Low- load	Each set until failure	• Light weights	Whole body	Improve fatigue toleranceHypertrophyStrength gain	 Greater exercise volume required for adaptation Discomfort and high-effort at lifting failure
		BFR (each set until near or true failure)	Light weightsBFR device	Upper and lower limb	• Reduce exercise volume and number of sessions required for adaptations	 Perceptual pain from BFR Discomfort near or at lifting failure
Endurance training	Cycling	Non-BFR	• Cycle ergometer • Bicycle	Lower limb	 Familiar activity Hypertrophy and strength gain possible Cardiovascular fitness Less impact force (safe for joints) 	• Longer period required for adaptation than resistance training
		BFR	Cycle ergometerBicycleBFR device	Lower limb	• Reduce training period for adaptations	Perceptual pain from BFRAdditional cardiovascular stress
	Walking	Non-BFR		Lower limb	• Very easy and safe to perform • Familiar activity	 Small or minimal hypertrophy and strength gain Longest period required for adaptations Effective mainly for older adults
		BFR	• BFR device	Lower limb	 Shorter period required for adaptations than normal walking Effective for a wider range of muscles and ages 	 Perceptual pain from BFR Additional cardiovascular stress

Blood flow restriction is usually NOT applied during high-load resistance training because the blood flow is already restricted by the contraction of the exercising muscle itself. BFR, blood flow restriction. MH, muscle hypertrophy.

who are less enthusiastic about equipment-required resistance training. A disadvantage to walking/cycling training is that it appears to take a long time for significant functional and morphological adaptations occur. It also remains unclear whether low-load resistance training and endurance training can keep increasing muscle size for a prolonged period (e.g., over years) since the available data are based on studies carried out for several weeks or months. Finally, the forfeiture of mechanical stress during low-load training appears to require the counterbalancing effects of training to failure and restriction of blood flow both of which entail substantial effort and discomfort.

For those who are motivated and/or can tolerate it, high-load training methods continue to confer significant benefits. In particular, the advantages of high-load resistance training, such as greater strength gains, longerterm effects and less training volume required in both untrained and trained individuals should not be ignored. Thus, athletes and enthusiastic individuals are encouraged to undergo both mechanical and metabolic stress not only for maximized strength gain and hypertrophy, but also for improved fatigue tolerance.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this article.

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