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Blood flow restriction: An evidence based progressive model (Review)

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To remain independent and healthy, an important factor to consider is the maintenance of skeletal muscle mass. Inactivity leads to measurable changes in muscle and bone, reduces exercise capacity, impairs the immune system, and decreases the sensitivity to insulin. Therefore, maintaining physical activity is of great importance for skeletal muscle health. One form of structured physical activity is resistance training. Generally speaking, one needs to lift weights at approximately 70% of their one repetition maximum (1RM) to have noticeable increases in muscle size and strength. Although numerous positive effects are observed from heavy resistance training, some at risk populations (e.g. elderly, rehabilitating patients, etc.) might be advised not to perform high-load resistance training and may be limited to performance of low-load resistance exercise. A technique which applies pressure cuffs to the limbs causing blood flow restriction (BFR) has been shown to attenuate atrophy and when combined with low intensity exercise has resulted in an increase in both muscle size and strength across different age groups. We have provided an evidence based model of progression from bed rest to higher load resistance training, based largely on BFR literature concentrating on more at risk populations, to highlight a possible path to recovery.

Keywords: KAATSU, occlusion training, elderly, rehabilitation

To remain functionally independent and healthy, an important factor to consider is the maintenance of skeletal muscle mass. Skeletal muscle is a highly plastic tissue capable of responding to an appropriate stimulus by signaling growth and strength gains. Furthermore, skeletal muscle functions as the largest disposal site of ingested glucose (35), plays an important role in lipid oxidation (33, 82), and is one of the greatest modifiable contributors to the resting metabolic rate (RMR) (9), highlighting the importance of maintaining skeletal muscle quantity and quality. In contrast, physical inactivity leads to muscle atrophy which itself is associated with numerous health consequences. Inactivity caused by an unloading of body weight can lead to measurable changes in both the quantity and quality of muscle and bone, reduced exercise capacity, an impaired immune system, and decreased sensitivity to insulin (8). These periods of reduced ambulatory activity are common following surgery or injury, and a recent hypothesis suggests that acute periods of inactivity may accelerate the development of sarcopenia (18). Additionally, a recent bed rest study suggested that 7 days of physical inactivity induced unfavorable changes in skeletal muscle metabolic capacity and

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negatively affected the exercise induced gene response, which may ultimately interfere with the ability of the muscle to adapt to exercise (81). All together these findings highlight the importance of maintaining physical activity and skeletal muscle health.

One form of a structured physical activity program is resistance training. Generally speaking, one needs to lift weights at approximately 70% of their one repetition maximum (1RM) to have noticeable increases in muscle size and strength (5). This recommendation is true for both genders and across different age groups. Although numerous positive effects have been observed from heavy resistance training, some populations (e.g. elderly, rehabilitating patients, etc.) might be advised not to perform high-load resistance training and may be limited to performance of low-load resistance exercise. Although some exercise is likely better than none from a metabolic health standpoint, heavy loading is typically required to induce muscle hypertrophy (5).

Interestingly, a technique which applies blood flow restriction (BFR) alone to the limbs has been shown to attenuate muscle atrophy (45, 46, 90) and when combined with low intensity exercise, this technique has resulted in an increase in both muscle size and strength across different age groups (61). BFR is applied with the intent to restrict arterial blood flow into the muscle of interest and occlude venous outflow of that muscle, resulting in venous pooling. In addition, this technique appears to offer no greater health risk than training with high loads (62) while greatly reducing mechanical stress to the joints. Furthermore, several studies indicate that this method of training may also positively influence the quality and quantity of bone (3, 6, 7, 41). The increase in intramedullary pressure and interstitial fluid flow within the bone caused by venous occlusion is a likely mechanism behind the positive effects observed in bone with exercise combined with BFR (63).

It has been hypothesized that this training technique would be beneficial for those who are unable to perform exercise with high loads (59), however, no progression model or recommendations for any form of progressive overload have been made for utilizing this method of training in a clinical or a rehabilitation setting. Based on previously published studies, we offer the idea for an evidenced based progressive model to recovery through differing phases of physical abilities (Table I) with the overall goal of maintaining or increasing muscle mass and strength during each phase. In addition, we provide the potential physiological mechanisms involved for each particular phase.

Phase I-bed rest condition with BFR

An individual may be confined to bed rest following an illness, surgery, injury, or possibly in response to the fear of falling for the elderly (20). Although bed rest is often necessary to insure that further injury does not occur, studies have found that chronic bed rest has deleterious effects on overall muscle mass. To illustrate, prolonged bed rest increases nitrogen excretion and the source of this nitrogen is largely skeletal muscle (14, 15, 22, 85). Studies have found that although protein degradation is largely unaffected by bed rest (85, 87), protein synthesis is suppressed (22, 23). Bed rest causes a loss of muscle mass in the young (74), but the loss is much greater in the elderly (42).

If the individual is confined to bed rest, they are most likely unable to perform the very activity that helps maintain muscle mass and functional capacity. Recently, research with cast-immobilization suggests that the application of BFR alone, without exercise, is able to minimize changes in leg size and muscular strength (45, 46). Although this is not an identical

parallel to a bed rest condition, it does provide a useful human model for studying the effects of BFR on the attenuation of atrophy. To illustrate, Takarada et al. (90) found that the application of BFR was effective in diminishing the post-operative disuse atrophy normally seen in lower limb muscle following surgery. The patients who underwent anterior cruciate ligament surgery were placed into one of two groups. The control group followed the usual program for recovery in the hospital with their injured knee kept immobilized by a knee brace. The experimental group underwent the same treatment with the addition of BFR (5 minutes inflated, 3 minutes deflated, repeated 5 times; 9 cm wide cuff; ~238 mmHg) twice a day from the 3rd to the 14th days post-operation. Without the application of BFR, the cross-sectional area (measured by MRI) of the knee extensors and flexors decreased by 20% and 11%, respectively. With BFR, they both decreased but only approximately 9%, indicating that BFR may be an effective means to attenuate muscle atrophy.

Table I. Evidence supporting each progressive phase of blood flow restriction (BFR)

Authors	Population	Conclusion
PHASE I		
Takarada et al. (90)	Men and women; Post-ACL reconstruction (~22 yrs)	The BFR stimulus effectively diminishes the post-operation disuse atrophy of the knee extensors.
Kubota et al. (46)	Men; Cast immobilization (~23 yrs)	The BFR stimulus to the lower extremity prevents disuse muscular weakness.
Kubota et al. (45)	Men; Cast immobilization (~22 yrs)	The BFR stimulus of 50 mmHg to the lower extremity reduces muscular weakness induced by chronic unloading.
PHASE II		
Abe et al. (2)	Men (~21 yrs)	The combination of BFR with slow walk training induces muscle hypertrophy and strength gain, despite the minimal level of exercise intensity.
Abe et al. (4)	Men and women (60–78 yrs)	The combination of BFR with slow walk training did not simultaneously improve cardiovascular and muscular fitness. However, it did increase muscular size and strength as well as functional ability.
Abe et al. (3)	Men and women (60–78 yrs)	Slow walk training combined with BFR increased muscle size and strength when performed 5x/week. Furthermore, a 2x/week training regimen can maintain the training response over an additional 12 week period.
Abe et al. (1)	Men (20–26 yrs)	Low-intensity, short duration cycling exercise combined with BFR improves muscle hypertrophy and aerobic capacity concurrently.
Iida et al. (38)	Women (59–78 yrs)	Walk training with BFR increased limb venous compliance.
Ozaki et al. (72)	Men and Women (57–76 yrs)	Walk training with BFR can improve thigh muscle size and strength as well as carotid arterial compliance.
Ozaki et al. (73)	Women (57–73 yrs)	BFR walk training improves both muscle volume and strength in older women.

Table I continued

Authors	Population	Conclusion
PHASE III		
Takarada et al. (91)	Postmenopausal women (~58 yrs)	Low intensity resistance exercise with moderate BFR caused marked muscular hypertrophy and strength gains in the elbow flexors.
Ohta et al. (71)	Men and women; Post-ACL reconstruction (~20 yrs)	Moderate BFR with low-load resistance training is an effective exercise for positive skeletal muscle adaptation.
Sata (83)	Male; Patella tendinitis patient (17 yrs)	BFR resistance training is useful for the treatment of patella tendonitis and transitioning the athlete back to active participation.
Cook et al. (13)	Men and women; Limb suspension (18–50 yrs)	Low-load resistance training with BFR is effective in maintain size and strength during 30 days of unloading and results in improved muscular endurance.
Evans et al. (19)	Men (20 yrs)	BFR resistance training increased strength as well as micro-vascular filtration capacity.
Gualano et al. (28)	Male; Idiopathic inflammatory myopathy (65 yrs)	BFR in combination with resistance training lead to improvements in muscle function and quality of life, without inducing disease flare.
Karabulut et al. (40)	Men (50–64 yrs)	BFR training was as effective as high intensity traditional resistance training in terms of the magnitude and pattern of change in muscular strength.
Karabulut et al. (41)	Men (56 yrs)	BFR in combination with low load resistance training enhanced strength and resulted in bone marker responses suggestive of bone formation.
Lejkowski et al. (51)	Female; Post-ACL reconstruction (19 yrs)	Low-load resistance training with BFR maintained post-surgical muscle size and subjective knee function.
Patterson et al. (76)	Men and women (62–73 yrs)	Low-load resistance training with BFR may be beneficial to older individuals to improve strength and blood-flow parameters.
Yokokawa et al. (97)	Men and women (~72 yrs)	Low-load resistance training with BFR improved physical function, especially muscular strength.
PHASE IV		
Yamanaka et al. (94)	Men (19 yrs)	Low-load BFR training increased size and strength when done in conjunction with traditional higher load training. This effect was more pronounced than the non-BFR training group which also performed higher load training.
Yasuda et al. (96)	Men (22–32 yrs)	Improvements in isometric and dynamic strength were greater when combining low load BFR training with higher load training. A combination of both maybe more of an effective training program for promoting strength than low load BFR only.

In a follow-up study using healthy subjects undergoing cast immobilization, Kubota et al. (46) found that the application of BFR (200 mmHg) twice a day for 14 days (5 minutes inflated, 3 minutes deflated, repeated 5 times; 7.7 cm wide cuff) was able to prevent both muscle weakness (knee extension and knee flexion) and decreases in thigh and leg circumference. In comparison, the other two groups in this study, including one group which performed isometric exercise (20 repetitions; 5 second contraction, 5 second rest), were not able to prevent complete losses in either strength or thigh and leg circumference. The use of thigh and leg circumference as their sole measurement of atrophy was a limitation; however, the maintenance of strength indicates a beneficial response to the application of BFR. More recently, Kubota et al. (45) reported that a pressure as low as 50 mmHg reduced losses in strength from cast immobilization, indicating that BFR alone is beneficial for maintaining muscular function during times of unloading (45).

Although the primary focus of this paper is maintaining muscle mass and strength, it should be noted that the application of BFR alone also produces a pronounced cardiovascular response. Nakajima et al. (68) observed that when BFR was applied during 24 hours of bed rest (6° head down tilt), the responses of heart rate, stroke volume, noradrenaline, anti-diuretic hormone and plasma renin activity produced the same effects as standing, thus stimulating a gravity-like stress during bed rest. This is of importance because when bed rest is prolonged, the body responds to the lowered cardiac load with eccentric cardiac atrophy (16, 77) and a decrease in left ventricle compliance (52, 78). Therefore, BFR may provide not only a countermeasure to muscle atrophy, but also to cardiovascular deconditioning (68).

In summation, during periods of bed rest we propose that the application of BFR may be a possible modality to maintain muscle mass, strength and orthostatic tolerance. As a patient becomes stronger, but still unable to be ambulatory, we propose supine bodyweight exercise be added to the BFR (86) in order to help facilitate the adaptation of muscle and lead to increased exercise capacity. It should be acknowledged that these BFR studies have been completed on overall healthy subjects (i.e. other than ACL injury), therefore it could be speculated that the application of BFR may be even more advantageous for older sedentary subjects who have already undergone extensive deterioration in functional capacity, resulting in them being confined to bed rest. Although not known, it may be that in these populations the application of BFR alone may actually illicit an increase in muscle mass. Irrespective, once the individual is capable of ambulation, they should be progressed to Phase II of this progressive training model.

Phase I-mechanisms

The mechanisms behind the beneficial muscle adaptions observed with BFR, particularly without exercise, are not completely known. Preliminary research from our laboratory suggests that muscle cell swelling may be playing some role. For example, decreases in plasma volume and increases in muscle size are observed following the application of BFR alone (unpublished observations). The increases in muscle size are maintained at least 3 minutes following the removal of BFR, suggesting that the increase in muscle size was not due to venous pooling and may have been due to a fluid shift from the plasma to the muscle. The theory behind the cell swelling induced changes in protein anabolism and catabolism was first introduced by Haussinger et al. (32) in 1993. Based on Haussinger's hypothetical model for hepatocyte cell swelling (31), it has been theorized that BFR induced muscle cell swelling is detected by an intrinsic volume sensor. The activation of this volume sensor may

lead to an activation of the mammalian target of rapamycin (mTOR) and mitogen-activated protein-kinase (MAPK) pathways (55). These pathways are activated with BFR and exercise; however, it is unknown whether these pathways are activated in the absence of exercise.

Several possibilities exist for how BFR may induce an increase in muscle cell size, however, the exact mechanism(s) by which it may occur is not presently known. It is possible that BFR may increase the hydrostatic pressure gradient thereby increasing the intracellular water flux. In addition, although significant changes in whole blood lactate are not observed with BFR alone, it is possible that there is a slight decrease in intracellular pH which would lead to an increase in hydrogen ions. This is important because pH-regulating transporters working in parallel with each other have been previously observed to mediate cell volume changes (34). Another possibility is an increase in serum- and glucocorticoid-inducible kinase-1 (SGK1) which is upregulated by ischemic conditions and may play an important role in the regulation of muscle cell volume (48, 49). Although BFR does not exactly replicate the stress of ischemia, it is probable that there is a reduced rate of oxygen delivery.

Another mechanism which has been proposed for the maintenance of muscle mass with BFR in the absence of exercise is signaling through the β_2-adrenoceptor (90). Every study that has investigated the norepinephrine response to BFR with and without exercise has observed significant increases (36, 37, 39, 47, 65, 66, 68, 84, 88, 89, 92). The increase in norepinephrine with BFR alone is likely due to the unloading of both the arterial and cardiopulmonary baroreceptors from a decrease in venous return (17, 36). This increase may be physiologically important for muscle as research indicates that catecholamines may also have a positive effect on skeletal muscle protein metabolism (64), particularly when basal levels of protein synthesis are suppressed (69). Previous research has shown that limb immobilization decreases basal levels of muscle protein synthesis (79). Therefore, when Kubota et al. (45, 46) applied BFR to the immobilized limb, norepinephrine may have had a positive effect on muscle protein turnover through binding of the β_2-adrenoceptor (64).

In conclusion, it appears that the predominant mechanisms involved in maintaining skeletal muscle mass with BFR in the absence of exercise include muscle cell swelling and increased signaling through the β_2-adrenoceptor. Although indices of both variables have been observed with BFR, the signaling pathways involved for each are not known and remain speculative.

Phase II-low-intensity walking with BFR

The second phase of this model is a progression to low-intensity walking combined with BFR. Although greater gains in strength and muscle hypertrophy are observed with BFR resistance training (61), some individuals may not be physically able to perform those movements early in their rehabilitation. The authors recognize that gains in muscle size and strength have been previously observed with aerobic exercise in the elderly without BFR; however, the intensity used was approximately 60–80% of heart rate reserve (30). The benefit of the application of BFR is the resulting gains in muscle function at a much lower exercise intensity, which is likely initially more important for those who may be progressing from surgery or illness.

Treadmill walking with BFR (160–220 mmHg; 11 cm wide cuff) has previously been demonstrated to increase maximal oxygen consumption (VO_{2MAX}) (75) as well as to increase both skeletal muscle mass and strength (Abe et al. (2); 160–230 mmHg; 5 cm wide cuff; Ozaki et al. (73); 140–200 mmHg; 5 cm wide cuff). In addition, Ozaki et al. (72) found that 10 weeks of BFR treadmill walking in the elderly (~66 years) at 45% heart rate reserve

produced not only increases in muscular size and strength but also increased carotid arterial compliance. The change in arterial compliance was similar between treadmill walking with and without BFR, and there were no significant changes in carotid or brachial blood pressure at rest for either group before or after training.

If one is unable to progress directly to weight bearing treadmill walking or if one prefers to vary the mode of exercise, low-intensity cycling with BFR at 40% VO_{2MAX} has been previously demonstrated to increase muscle CSA (measured by MRI) and strength following 8 weeks of exercise (1). Alternating between cycling and treadmill walking with BFR offers variety to those who may prefer cycling to treadmill walking, but treadmill walking with BFR should still be performed as it is an important functional activity in completing many activities of daily living.

In conclusion, it is known that walking combined with BFR as little as twice per week is able to maintain muscle mass, strength, and positively influence markers of bone metabolism in the elderly (3). Furthermore, these improvements in skeletal muscle health have been extended to other "aerobic" like activities such as cycling (1). However, once an individual has gained significant increases in size and strength with BFR low-intensity walking and is physically able, the progression should continue to a mode of exercise known to exhibit greater gains in muscle size and strength such as low-load resistance training with BFR (Phase III).

Phase II-mechanisms

The proposed mechanisms for slow BFR walking are similar to the proposed mechanisms in Phase 1, however, the effect of norepinephrine on promoting muscle anabolism through the β_2-adrenoceptor is less likely in a limb that is not immobilized (98). Acute changes in muscle size have been observed with slow (56 m/min) and fast BFR walking (87 m/min) without a significant decrease in force (70), suggesting that muscle fatigue is not a prominent mechanism at these speeds. In addition, walking at slow speeds does not result in an accumulation of metabolites in the blood (75 m/min [60]) or a large increase in systemic hormones (50 m/min [2]). Therefore it appears that the predominant mechanism behind the benefits observed with BFR walking at low intensities may be the acute increase in muscle cell volume. Although metabolites are not significantly increased in the blood, it is probable that with BFR walking there are greater amounts of metabolites produced inside the muscle which may promote a greater fluid shift. Another probable explanation may be an increase in cardiac output or blood volume during BFR walking exercise which causes a greater accumulation of blood in the working muscle (venous pooling), possibly allowing a greater fluid shift into the muscle cell. This greater increase in cell size may explain why muscle hypertrophy is observed with low-intensity BFR walking, but not with BFR in the absence of exercise.

Phase III low-load resistance training with BFR

The third phase of this model is a progression to low-load resistance training combined with BFR. At this phase, it is recommended that treadmill walking/cycling with BFR be slowly phased out with the goal of making resistance training the primary modality for maintaining or increasing muscle size and strength. Numerous studies investigating low-load resistance training in combination with BFR have demonstrated efficacy with respect to skeletal muscle, but we will highlight only a few published reports that used more at risk populations (Table I).

Takarada et al. (91) investigated the long-term effects of low-load resistance training with BFR in post-menopausal women. Briefly, the women were divided into three groups and

completed 16 weeks of elbow flexor training. The groups included low-load training (30–50% 1RM) with and without BFR (3.3 cm wide cuff; ~110 mmHg) and a higher-load training group (50–80% 1RM). Following the 16 weeks, the low-load BFR group and the higher-load group had similar increases in muscle size and strength; however, the low-load group without BFR had no increase in either variable highlighting the benefit of the BFR stimulus.

Research from our group has confirmed this increase in muscle function in post-menopausal women using BFR in combination with resistance exercise utilizing elastic bands (unpublished observations). Furthermore, we have demonstrated, in older men, both increases in strength and improvements in markers of bone formation (40, 41) following low-load resistance training with BFR. Karabulut et al. (40) trained 37 older men for 6 weeks (3x/week) using either low loads (20% 1RM) with BFR (5 cm wide cuff; 160–240 mmHg) or high loads (80% 1RM) without BFR. Following training, both groups significantly increased muscular strength and the low-load protocol in combination with BFR was almost as effective at increasing strength as the higher-load training protocol (40). Furthermore, our group has also observed improvements in markers of bone formation with low-load BFR resistance training in older men, similar to that observed with high-load resistance training (41).

Although many of the recommendations for loading presented in this paper are relative to 1RM, those individuals unable to use high loads should initially base the exercise load on their perceptual responses to the exercise stimulus. In addition, the load in combination with BFR should be set, such that the exercise can be completed through a pain free range of motion. Furthermore, the exercise load should initially remain submaximal with the eventual goal of reaching the standard workloads for BFR protocols, 4 sets of exercise with 30, 15, 15 and 15 repetitions. Multiple studies have previously demonstrated success using similar methods (28, 71, 83). After establishing the standard workload of 75 repetitions, implementing BFR exercise to failure may also provide further adaptation, although it is likely advantageous to use a combination of both (i.e. submaximal and failure) for continuous progression. Our recommendation remains broad because specifics of each protocol will be dependent upon the functional capacity of the individual.

In conclusion, low-load resistance training with BFR has resulted in significant increases in muscle size and strength which have been observed across differing populations (Table I). Although it is not always possible for certain populations to return to resistance training with higher mechanical loads, that nevertheless should be the goal for most populations. For those capable of performing higher-load resistance training, they should transition into using BFR occasionally in combination with non-BFR higher-load training (Phase IV).

Phase IV-low-load in combination with high-load resistance training

High-load resistance training unequivocally results in positive adaptations in skeletal muscle size and strength, as well as overall improvements in functional performance (10, 24, 25). Favorable changes in tendon stiffness also occur with high-load isometric training (43), although, one study has found that tendon stiffness may not change with low-load isotonic BFR training (44). Therefore, if physically able, one should slowly start exercising more with a combination of low-load resistance BFR training and higher non BFR mechanical loads as this may ultimately be more beneficial than the adaptations resulting from each independent training phase. To date, only two studies have demonstrated the benefits of using low-load resistance BFR training in conjunction with higher-load resistance training.

Yasuda et al. (96) investigated this combination training with the chest press exercise by dividing subjects into three separate exercise groups and train them over a 6 week period

(3x/week). Groups included those working with a high load (75% 1RM), those working with a low-load (30% 1RM) BFR (100–130 mmHg), and a combination group which exercised with low load BFR 2x/week and high load 1x/week. All groups increased triceps brachii and pectoralis major CSA (measured by MRI), with no differences observed between groups. However, the functional performance results indicated that improvements in relative isometric (Nm/cm^2) and dynamic (kg/cm^2) strength brought about by combining low-load BFR training with high-load exercises were higher than those observed with only low load BFR. These findings may indicate that the strength increases for low-load BFR are due to muscle hypertrophy and not to neural adaptation. The benefits of this combined method of training have been further extended to include NCAA Division I American football players. Briefly, Yamanaka et al. (94) found that when low-load resistance training with BFR was added as a supplement to their existing high-load program, additional increases in strength and muscle girth were observed. These benefits exceeded those with the high-load program in combination with regular (no BFR) low-load training.

Although preliminary when compared with the amount of evidence for Phases II and III of this model, the results thus far indicate that low load BFR training combined with higher load training likely offers the best risk to reward ratio for improved muscle strength and mass. Once physical function has returned to normal levels, one may be ready to return to exclusively higher load resistance training, however, in our experience, many people, particularly those of advancing age, express little desire to train exclusively with higher loads. Therefore, the evidence exists, albeit preliminary at this time, to demonstrate that significant functional improvements can be observed with higher load training in as little as 1x/week when combined with low load training 2x/week with BFR (96). Therefore, one can either maintain Phase IV indefinitely or transition into exclusively non BFR high-load training.

Phase III/IV-mechanisms

Low-load resistance training with BFR is the most mechanistically studied form of BFR. Research thus far suggests that a prominent mechanism is likely the stimulation of muscle protein synthesis (26, 27, 29). This may occur from a reduced oxygen environment (not anoxic) and through metabolic accumulation which may increase the recruitment of higher threshold (Type II) fibers through the stimulation of groups III and IV afferent fibers (95). It is thought that accumulation of metabolites may also facilitate the increase in growth hormone observed following resistance exercise with BFR (89), although the muscle anabolic effect of growth hormone in adults is largely unfounded (80). In addition, research has observed that MuRF-1 (marker of protein breakdown), Atrogin-1 (marker of depressed protein synthesis), and myostatin expression are decreased following low-load resistance exercise in combination with BFR (50, 67).

Interestingly, recent data from Gundermann et al. (29) suggests that reactive hyperemia following the removal of BFR is not a likely mechanism for the increase in muscle protein synthesis, as administration of a pharmacological vasodilator following non-restricted low-load exercise was unable to reproduce the protein synthetic response observed following low-load BFR resistance training. In addition to increases in mTOR signaling, previous investigations have found that low-load resistance exercise with BFR results in concurrent activation of the MAPK signaling pathway (26, 29), suggesting that both mTOR and MAPK may be needed to induce a maximal muscle protein synthetic response following low-load BFR resistance exercise. In addition, Fry et al. (26) found an increase in an indirect marker

of cell swelling (thigh circumference) and hypothesized that cell swelling may have played a potential role with the increase in protein synthesis.

In conclusion, when BFR is combined with low-load resistance exercise the effects on both muscle hypertrophy and strength are likely augmented over Phases I/II by increases in the previously mentioned mechanisms (e.g. fiber type recruitment, hormones).

Mode of BFR and cuff pressure

A variety of devices have been used to restrict blood flow during exercise including elastic knee wraps (53), elastic belts with a pneumatic bag inside (21), nylon pneumatic cuffs (67), or a traditional nylon blood pressure cuff (93). Additionally, a range of restrictive cuff pressures have been used for restricting blood flow, generally ranging from approximately 1.3 times greater than systolic blood pressure (SBP; ~160 mmHg) to over 200 mmHg. We have recently shown that the cuff pressure may need to be individualized and based on the size of the limb and the width of the cuff and not necessarily on pressures previously used in the literature (e.g. bigger limbs require greater pressure) (56).

Over the past few years, research has also been completed on a BFR stimulus using elastic knee wraps (53, 54, 58, 60), which may broaden the populations capable of utilizing this technique as these are widely available. Although much research has focused on acute responses, a recently published training study using elastic knee wraps reported increases in muscle girth and strength in well-trained athletes (94). In addition, a bodybuilder recovering from an osteochondral fracture has recently used elastic knee wraps and a progression model similar to the one found in this paper to successfully rehabilitate back to predominately high load resistance training (manuscript under review). The chronic training adaptations to BFR with knee wraps is currently being investigated, to confirm the acute studies as well as the chronic study by Yamanaka et al. (94).

In conclusion, from a physiological standpoint, the magnitude of reductions in arterial and venous blood flow appear important, but not necessarily the device used to restrict blood flow. The pressure will be dependent upon limb size and the width of the cuff used (56), with the overall purpose to occlude only venous blood flow from the muscle and not arterial blood flow into the muscle.

Low-load exercise to muscular failure?

An important consideration to stress, particularly with at risk populations, is the necessity of keeping the exercise stimulus submaximal in nature, at least initially. To illustrate, acute research using low loads to failure (without BFR) have observed equivalent increases in myofibrillar protein synthesis when compared to exercise of higher loads (12); possibly through an increased time under tension (11). This has led some researchers to question the necessity of BFR. However, exercise to muscular failure is by definition not submaximal, which is an important factor to consider for populations who are not capable of exercising at higher intensities. Furthermore, exercise without BFR requires significantly more repetitions to be performed (57), which increases stress to the joint architecture. It must also be acknowledged that although these acute studies are hypothesized to be predictive of chronic adaptations, they are not definitive as incongruences may exist between acute and chronic changes following resistance training. In addition, protein degradation was not measured in either of the aforementioned studies, since the investigators completed their research under the assumption that synthesis rates and not degradation rates are more responsive to resistance exercise in healthy humans (80).

Perspectives

The information presented in this manuscript was written with the intent to present the idea for an evidence based model of progression. Until now, previous manuscripts have provided no progression model or recommendations for utilizing this method of training in a clinical or a rehabilitation setting. We have highlighted differing proposed phases of recovery ranging from zero activity with BFR alone to the last phase which is a combination of low-load BFR training with regular high-load non BFR resistance training (Fig. 1). In addition, we have provided evidence that submaximal BFR training is an effective stimulus for maintaining or increasing muscle size and strength, particularly for those who may be unable to exercise at higher intensities. Furthermore, we have provided discussion regarding the potential mechanisms of action for each phase. This is important, because the mechanisms present during low-load BFR resistance training are not always present with slow BFR walking nor are they present with BFR in the absence of exercise.

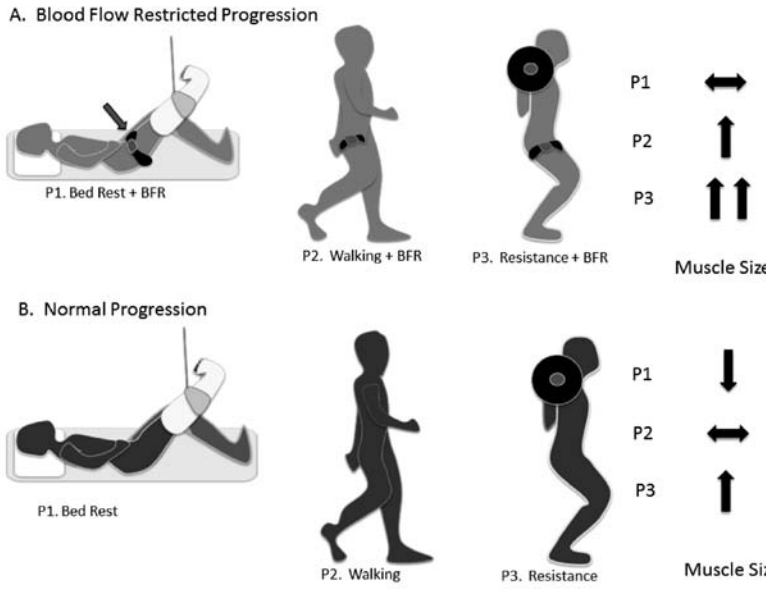

Fig. 1. Blood flow restricted versus general progression from bed rest to walking following a limb immobilizing injury. (A) The progression from bed rest with blood flow restriction (P1 = Phase I), followed by walking with blood flow restriction (P2 = Phase II), followed by resistance exercise with blood flow restriction (P3 = Phase III). Muscle size changes are depicted to the right of Figure 1A, and demonstrate the direction of change following each phase. (B) The normal progression from bed rest to walking following a limb immobilizing injury. P1–P3 are the same as Figure 1A without any form of blood flow restriction. Muscle size changes are depicted to the right of Figure 1B, and demonstrate the direction of change following each phase

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