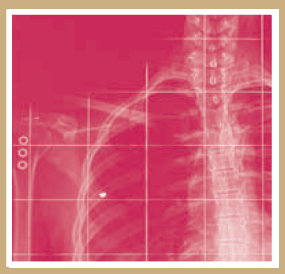

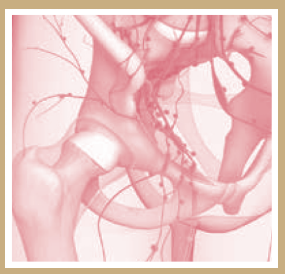

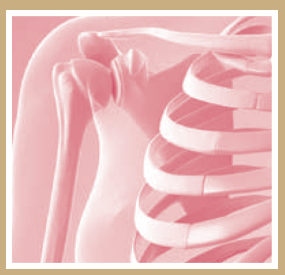

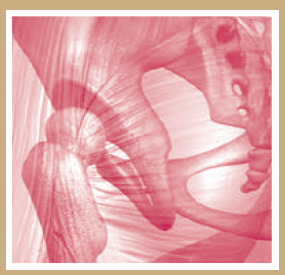

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Translational and Surgical Techniques

BFR Training: Current and Future Applications for the Rehabilitation of Musculoskeletal Injuries

Guest Editors
John S. Mason, PT, DSc, SCS, CSCS
Johnny G. Owens, MPT
William J. Brown, PhD, RN, FNP-BC

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Blood Flow Restriction Training: Current and Future Applications for the Rehabilitation of Musculoskeletal Injuries

MAJ John S. Mason, PT, DSc, SCS, CSCS, Johnny G. Owens, MPT,† and LTC William J. Brown, PhD, RN, FNP-BC**

Science continues to examine interventions to improve fitness, delay age-related decrements in physical function and facilitate healing and recovery after injury. These factors, or lack thereof, directly affect not only quality of life, but also the overall health care financial burden. With a surging population of seniors 65 years and older, which will swell to over 98 million by 2060, the need for interventions that may mitigate senescent changes could not be timelier. Orthopedic surgeons face many challenges in providing care to not only an aging population, but also to a younger subset that is highly active and engaged in a variety of high-impact sports. Therefore, interventions that can positively affect patient health-related outcomes from the time of injury throughout the rehabilitation process are highly warranted.

This special issue will examine a novel but increasingly popular intervention, blood flow restriction (BFR) training. BFR training utilizes an automated pressure cuff placed on the proximal limbs to restrict blood flow and, when combined with light resistance exercise, produces a variety of positive physiological effects. BFR shows potential as an adjunct strategy postinjury or surgery to improve general physical conditioning, target muscle weakness around affected joints and hasten recovery. Moreover, BFR may also benefit the geriatric patient by mitigating age-related decrements in physical function. The following 6 articles will provide the reader with important information about the science, safety, and implementation of BFR training.

From a health and safety perspective, Dr Loenneke and colleagues provide a thorough review of the mechanisms and science behind BFR training. Although the mechanisms are not fully understood, this paper serves as a well-crafted summary on current best evidence for the adaptations being seen via BFR. Similarly, Dr Cahalin and colleagues have expanded the review on safety to higher risk patients with hypertension. With the aging baby boomer population likely to continue to seek orthopedic care, this article describes what is currently published and the scientific understanding of applying BFR in the hypertensive patient.

A primary concern during periods of disuse is the ensuing muscle atrophy that occurs. Dr Lambert and colleagues describe the potential ability of BFR to upregulate muscle protein metabolism and anabolic signaling to slow or reverse the catabolic postsurgery/injury state. Dr Hackney and colleagues discuss BFR as an intervention to mitigate age-related muscle loss (sarcopenia) and strength (dynapenia) within an aging population that can be implemented both preoperatively and postoperatively to hasten recovery following orthopedic procedures.

Anterior cruciate ligament (ACL) reconstruction is a common orthopedic surgery. Dr Patterson and colleagues describe the application of BFR after ACL reconstruction. There are currently multiple clinical trials worldwide assessing the addition of BFR to ACL rehabilitation. This paper describes the rationale for the addition of BFR postsurgically, the state of the current evidence and a sample clinical protocol. Finally, Dr Bradner and colleagues have provided a thorough review on the reported side effects and safety of BFR.

As this technique becomes more widespread, it is important for clinicians to understand the current applications, limitations, and safety considerations in order to effectively apply this modality to appropriate patients. Finally, we would like to thank all the authors for their time and contributions to this symposium.

From the *Womack Army Medical Center; and †Owens Recovery Science Inc., FT Bragg, NC.

The views expressed herein are those of the authors and do not reflect the official policy of the Department of the Army, Department of Defense, or the U.S. Government.

J.G.O. is a medical consultant for Delfi Medical Innovations, Inc and research consultant for METRC.

The authors declare that they have nothing to disclose.

Mechanisms of Blood Flow Restriction: The New Testament

Matthew B. Jessee, MSc, Kevin T. Mattocks, MSc, Samuel L. Buckner, MSc, Scott J. Dankel, MSc, J. Grant Mouser, MSc, Takashi Abe, PhD, and Jeremy P. Loenneke, PhD

Summary: When restricting blood flow for the purpose of increasing or maintaining muscle fitness, the aim is to reduce the amount of arterial flow into the limb and restrict the venous flow out of the limb. Doing so has been shown to elicit positive adaptations with regards to skeletal muscle size, and strength, while some evidence also eludes to beneficial effects on vascular and bone tissue. Regarding skeletal muscle, the main benefits of blood flow restriction are the ability to stimulate increases in size and strength while avoiding the greater mechanical stress associated with traditional high-load resistance training, and the greater volumes required when exercising with low loads to failure. While the most robust benefits are observed following blood flow restriction during low-load resistance training, evidence suggests positive adaptations occur while restricting blood flow during low-intensity aerobic exercise, and perhaps even during periods of disuse in the absence of exercise. Although the exact mechanisms are unclear, most of the evidence seems to allude to cell swelling and metabolite-induced fatigue during exercise stimulating synthetic pathways that can lead to muscle growth. While the blood flow restriction stimulus has been shown to be relatively safe for participants, the practitioner should be cognizant of the relative pressure being applied to the underlying tissue. This is important as cuff type, cuff width, and limb circumference can all influence the restrictive stimulus. Therefore, to ensure a similar, safe stimulus all variables should be accounted for.

Key Words: vascular occlusion—ischemia—Kaatsu—low load—volitional failure.

(*Tech Orthop* 2018;33: 72–79)

WHAT IS BLOOD FLOW RESTRICTION?

The benefits of blood flow restriction as they relate to skeletal muscle were first reported in the literature by Shinohara et al.[1] in 1998. The authors observed that isometric training for 4 weeks at a relatively low intensity (40% of maximal voluntary contraction) increased strength to a greater magnitude when training under blood flow restriction versus the same training with no restriction. The initial justification behind applying blood flow restriction during exercise was essentially to create a metabolic environment capable of altering neuromuscular activity through afferent feedback. This metabolic environment is created by applying a restrictive device on the proximal portion of a limb to reduce the amount of arterial blood flow (possibly creating a more hypoxic environment), and to occlude venous return, which results in a pooling of blood and metabolic byproducts distal to the restriction.[2] Since the initial investigation by Shinohara et al,[1] the application of blood flow restriction has been shown to increase not only skeletal muscle size[3,4] and strength,[5,6] but possibly induce positive vascular[7] and bone[8] adaptations as well. These beneficial effects do not seem to be limited to specific populations, as they have been observed in a variety of individuals, such as the injured,[9] elderly,[4,10] healthy untrained,[3,6] and athletes.[11–13] Although some speculation exists pertaining to the safety of the technique, blood flow restriction does not seem to augment the health risk over and above that of traditional aerobic or resistance exercise modalities.[14] Therefore, blood flow restriction training seems to be a safe and effective alternative to traditional high-load training as it lowers the mechanical stress (ie, the stress placed upon the tissues from higher external load) needed to elicit adaptation.[15] However, the response may depend on the mode of restriction as it can be utilized in a variety of settings, including blood flow restriction applied alone,[9,16] in combination with electrical stimulation,[17] aerobic exercise,[5,18,19] or various types of resistance exercise.[3,7,20,21]

BENEFITS OF BLOOD FLOW RESTRICTION—ALONE, ELECTROSTIMULATION, AEROBIC, RESISTANCE

Blood Flow Restriction Alone

Blood flow restriction has been suggested as a technique to be used to augment muscle adaptations during all phases of the rehabilitative process, including bedrest.[22] Since disuse atrophy and muscular weakness can occur relatively quickly in response to immobilization, it is imperative to recover ambulation as soon as possible.[23] However, physical activity may be delayed or contraindicated depending upon the stage of recovery. In such a case, blood flow restriction presents a potentially useful stimulus to slow the rate of atrophy and maintain muscular strength. In the absence of exercise, a series of inflations and deflations of a restrictive cuff placed at the top of the thigh attenuates muscle atrophy in patients undergoing anterior cruciate ligament reconstruction,[9] as well as maintains a higher level of strength over a control group during a 2-week period of immobilization,[24] even when applying a low absolute pressure.[16] In contrast, Iversen et al[25] found no beneficial effect of blood flow restriction over a control group when comparing muscle cross-sectional area following anterior cruciate ligament surgery in athletes. Whether this particular application of blood flow restriction is population specific remains to be investigated, but it should be noted the control group had an average time from injury to surgery 3 months greater than the blood flow restriction group. Since losses of lean mass can occur within just 2 weeks of reduced activity[26] it is possible the control group already had a slowed rate of muscle loss, thus leading to no difference between the groups. While blood flow restriction applied in the absence of exercise has only slowed the loss of muscle mass and strength in humans, adding neuromuscular electrostimulation may reverse the process, as evidenced by increased muscle thickness and strength following

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The authors declare that they have nothing to disclose.

For reprint requests, or additional information and guidance on the techniques described in the article, please contact Jeremy P. Loenneke, PhD, at jploenne@olemiss.edu or by mail at The University of Mississippi, P.O. Box 1848, University, MS 38677. You may inquire whether the author(s) will agree to phone conferences and/or visits regarding these techniques.

blood flow restriction electrostimulation training compared with a group receiving electrostimulation training alone.[17] It should be noted, however, that the participants were healthy and ambulatory with no immobilization. In a population of patients with spinal cord injuries, electrostimulation increased muscle size and strength in the wrist extensors, but when adding blood flow restriction, the muscle growth was greater compared with using electrostimulation alone.[27] If the application of blood flow restriction in the absence of any voluntary muscle activation proves to have positive musculoskeletal benefits for those recovering from surgery or immobilization, it could offer a unique stimulus to minimize the negative effects of disuse, and prepare an individual for ambulation.

Blood Flow Restriction With Aerobic Exercise

Although not normally associated with hypertrophy, aerobic exercise at low intensities can increase muscle size[28] and strength[29] when combined with blood flow restriction. In a group of young men, walk training at a speed of 50 m/min (< 20% VO_{2max}) while undergoing blood flow restriction twice a day for 3 weeks resulted in greater muscle cross-sectional area, isometric strength, and 1RM performance when compared with a work-matched control.[5] Similar results have been found in older women after 10 weeks of blood flow restricted walking 4 days per week at 45% of heart rate reserve.[30] In addition to muscular adaptations, cardiovascular improvements such as increases in aerobic capacity may be achieved when adding blood flow restriction to an 8-week cycling program at 40% VO_{2max}, whereas just cycling alone did not elicit any improvement in muscle size, strength, VO_{2max}, or time until exhaustion.[18] Therefore, for individuals capable of low-intensity activity, such as walking or cycling, adding blood flow restriction to a training program may augment the ability to induce positive muscular and cardiovascular adaptations, although not all investigations have shown these beneficial effects. A 6-week, low-intensity cycling protocol in young physically active men found no additional benefit of adding blood flow restriction with regards to VO_{2max}, muscle size, or muscle strength (apart from knee flexion) when compared with a nonexercise control.[31] These incompatible findings require further research to decipher whether the effects of blood flow restriction during aerobic exercise are population specific, or whether methodological differences contribute to the discrepancies. For instance, the intensity level of exercise may have been too low for an already active population of young men in the study by Kim et al[31] even though it may be sufficient for inducing muscle hypertrophy in elderly populations.[19,30] According to the authors, the prescribed cycling intensity was set at 30% of heart rate reserve, whereas previous studies, which based the training protocol on VO_{2max}, were performed at approximately 45% to 59% of heart rate reserve. Therefore, an intensity threshold may exist that must be reached for a healthy, active population to achieve beneficial muscular adaptation, even when undergoing blood flow restriction. Despite some conflicting results, the overall body of evidence seems to show that aerobic exercise training, while applying blood flow restriction, may induce positive changes in skeletal muscle size and strength for some populations.

Blood Flow Restriction With Resistance Exercise

Traditionally, to see the greatest increases in muscle size and strength it is recommended that an individual lift a relatively higher load, at least 60% 1RM,[32] but due to the greater levels of mechanical stress placed upon the tissues, this type of training modality may be contraindicated for certain populations. Interestingly, blood flow restriction combined with resistance training, using loads as low as 20% 1RM, produces similar gains in muscle size and strength as high-load (80% 1RM) resistance training,[6] making blood flow restriction a viable alternative to traditional resistance training. It should be noted that resistance training with loads as low as 30% 1RM without blood flow restriction can also induce similar increases in muscle volume to that of high-load training, provided exercise is performed to failure.[33] To illustrate, when comparing low-load resistance training that is work matched to a high-load resistance training protocol, muscle hypertrophy of the low-load work-matched group is often less than that of the high-load group[34]; but when taking the low-load resistance training to volitional failure, the hypertrophic differences are diminished and muscle growth is similar.[33] Low loads to failure alone are therefore effective for increasing muscle size. Thus, blood flow restriction may not be required to elicit muscle hypertrophy, but may still be preferred in situations where less overall work is desirable. Restricting blood flow during low-load exercise reduces the amount of work that must be performed to reach volitional failure thereby reducing the time that the musculoskeletal system is under mechanical stress while still resulting in similar muscle growth as traditional low loads to failure.[35,36] Of further benefit may be the greater strength increases observed following blood flow restriction training compared with training with a low load alone.[1] Thus, blood flow restriction presents an effective modality to precipitate muscular adaptation in a wide range of populations that may not be able to tolerate the mechanical stress associated with high-load training or greater exercise volumes associated with low-load training to failure.

MECHANISMS OF HYPERTROPHY

There are a variety of physiological mechanisms that are thought to provoke a hypertrophic response in skeletal muscle following blood flow restriction. Although the exact mechanisms remain unknown, most evidence seems to allude to a muscle cell swelling response and the indirect effect of metabolites, instigating an increased muscle activation through fatigue. Regardless of the initial signaling mechanism, for a muscle to grow the intracellular environment should favor a positive protein balance, achieved through an increase in muscle protein synthesis, a decrease in muscle protein breakdown, or both. Blood flow restriction training may be inducing hypertrophy through increasing the translation of proteins, as resistance exercise with 20% 1RM while undergoing blood flow restriction has been shown to increase muscle protein synthesis over a load-matched control condition with no restriction.[37] However, when rapamycin is administered before blood flow restriction exercise the expected increase in protein synthesis is blunted.[38] This is important, as rapamycin interferes with the mechanistic target of rapamycin complex 1 (mTORC1), which signals downstream pathways to increase the synthesis of proteins from mRNA.[39,40] This finding suggests that the effect of blood flow restriction exercise on muscle protein synthesis is mediated by mTORC1. Like traditional high-load training,[41] low-load resistance exercise while under blood flow restriction has been shown to phosphorylate proteins downstream of mTORC1, such as ribosomal protein S6 kinase beta-1 (S6K1), which is an important promoter of protein synthesis.[42] Blood flow restriction alone may also stimulate the mTORC1 pathway in the absence of exercise, as evidenced by the phosphorylation of downstream targets.[43] It should be noted that secondary pathways, such as mitogen-activated protein kinase pathways, similar to mTORC1, can stimulate mediators of protein synthesis,[44] and have also been upregulated in rodent models following blood flow restriction alone,[45] as well as in humans following blood flow restriction resistance exercise.[42]

Cell Swelling and Metabolite-induced Fatigue

Two major mechanisms thought to be driving skeletal muscle adaptation following blood flow restriction are cell swelling[20,46] and metabolite-induced fatigue.[2] Applying blood flow restriction in the absence of exercise results in acute increases in the thickness of muscles distal to restriction, along with comparable decreases in plasma volume that remain after cuff deflation.[20] This suggests that restriction may drive fluid into the muscle, possibly inducing a swelling response (Fig. 1). Cell swelling could inhibit protein breakdown or increase protein synthesis, resulting in a positive protein balance, which has been shown previously in hepatocytes.[46] In fact, applying blood flow restriction alone in a rodent model increases phosphorylation of S6K1 in the muscle, a regulator of protein synthesis, 1 hour postrestriction.[43] The potential importance of the greater accumulation of metabolites during blood flow restriction seems to be that they induce neuromuscular fatigue earlier than low-load exercise alone through the metabolic stimulation of group III and IV afferent fibers,[47] or inhibition of crossbridge cycling.[48] Thus, to continue exercise, higher threshold motor units are recruited,[49] resulting in a hypertrophic mechanical stimulus for a greater proportion of total muscle fibers (Fig. 2). Dankel et al[50] highlights the importance of taking exercise to failure in order to make the stimulus between different training modalities, such as low load and high load, more comparable. This concept is supported by comparing the muscle protein synthetic response between a high-load exercise condition, a low-load condition work matched to the high-load condition, and a low load to failure condition.[51] The low load to failure and high-load group had similar protein synthetic responses, which were greater than the low-load work-matched groups, suggesting the long-term changes in muscle size would be similar. Following a knee extension training program using both high-load and low-load exercise, the muscle growth observed was no different between a high-load condition and a low-load condition when both groups performed 3 sets to failure over 10 weeks.[33]

Metabolites

When coupled with exercise, the application of blood flow restriction results in an accumulation of metabolic byproducts within the working limb.[2] It has previously been suggested that the metabolites themselves may be directly augmenting muscle growth by stimulating anabolic hormonal pathways,[52] but this would not explain the hypertrophy seen with low-intensity blood flow restriction walking,[5] as a replication study found no measurable increase in metabolites following this particular protocol.[53] Furthermore, there was no association between the acute changes in hormones and the hypertrophy observed in response to walk training.[54] This still does not exclude the possibility that even though metabolites may not be required, they may augment muscle growth. However, an investigation in to the role of metabolites and muscle growth found that an 8-week training protocol using blood flow restriction to pool metabolites in the arm following a set of high-load elbow flexion exercise resulted in no increase in muscle size over that observed with exercise alone in the contralateral arm.[55] In fact, restricting blood flow postexercise seemed to have blunted the growth response in females, further suggesting that the metabolites themselves are not adding to the muscle growth response following high-load resistance exercise. Although a direct role of metabolites influencing muscle growth seems unlikely, they may be playing a large role indirectly by expediting the time it takes for muscle fibers to fatigue.

Systemic Hormones

The acute increase in systemic hormones such as growth hormone and testosterone following resistance training exercise has been purported to be important for increasing skeletal muscle size in response to a traditional high-load training program.[56] The systemic hormonal response, specifically that of growth hormone, to blood flow restriction exercise has been shown to be similar to the response following high-load exercise in young men and older men,[57] as well as in young women.[58] Following a 12-week, within-subject resistance training program comparing high-load and low-load blood flow restriction exercise on separate days, the increase in muscle size and strength did not differ due to condition, nor was the acute hormonal response different.[59] Although this may suggest that a similar hormonal response to exercise negates any differences in muscle growth, the authors did not explicitly investigate the relationship between the acute hormonal response and long-term adaptations. As within-subject control studies have shown, muscle size in the nonexercise control limb is not increased due to the contralateral

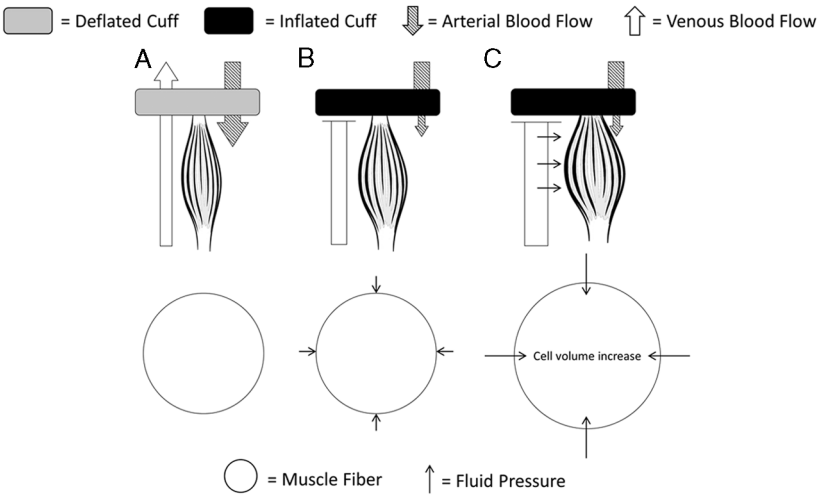

FIGURE 1. A, When applying an inelastic nylon cuff with no inflation, the restriction placed upon the tissue underneath the cuff is minimal, therefore there is little influence on blood flow. B, Upon inflation of the cuff to a relative pressure, arterial blood flow is reduced and venous blood flow is occluded causing blood to start pooling in the limb distal to the restriction. C, Prolonged occlusion of venous blood flow results in a pooling of fluid distal to the cuff, increasing the hydrostatic and osmotic gradients, driving fluid in to the muscle cells, and signaling regulators of protein balance. Muscle image used courtesy of https://www.aic.cuhk.edu.hk/web8/Muscle.htm.

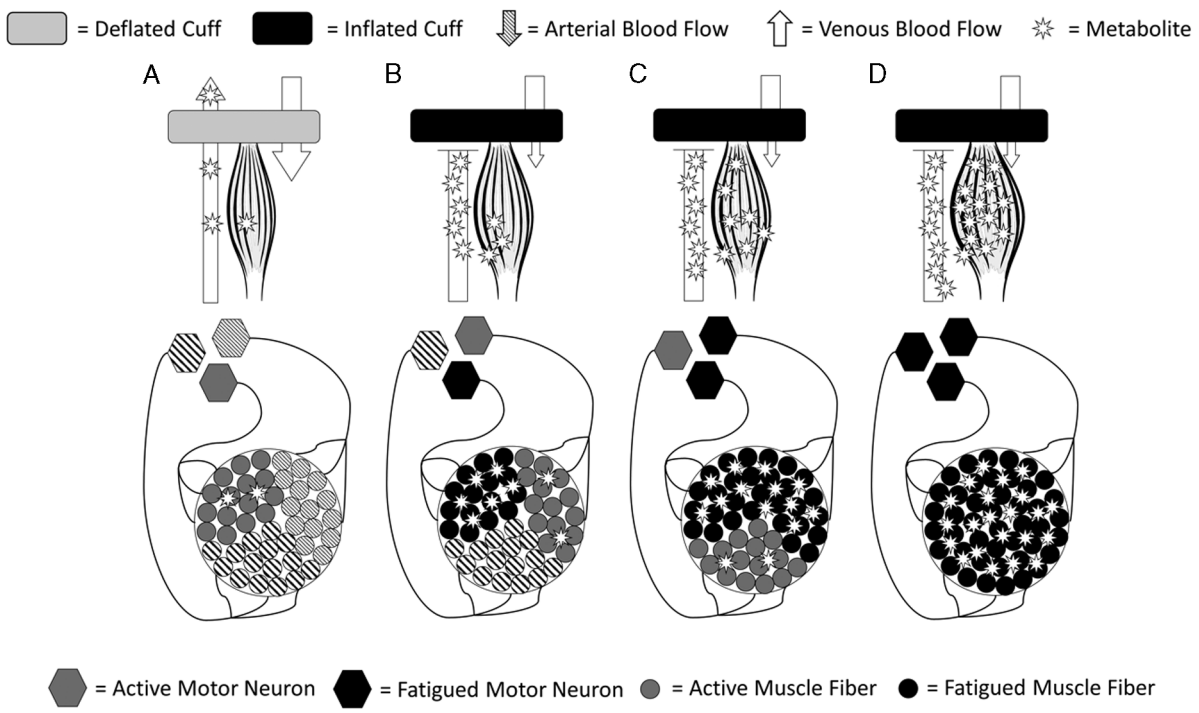

FIGURE 2. A, During low-load exercise with no cuff inflation, there are small disruptions in blood flow; however, given the magnitude of intramuscular pressure generated by low force contractions there is still a sufficient metabolite clearance and delivery of oxygenated blood to the working muscle, thus, exercise can be prolonged using a small proportion of the total muscle fibers. B, When applying blood flow restriction via inflation of the cuff, oxygenated arterial blood flow is reduced and venous blood flow is restricted, which results in less efficient clearance of metabolic byproducts distal to the cuff and fatigue of active fibers. C, As exercise continues the buildup of metabolic byproducts in and around the working muscle fibers interferes with the active motor units, thus to continue exercise, higher threshold motor units must be activated. D, The continued exercise and buildup of metabolites results in a greater proportion of muscle fibers being fatigued more quickly, resulting in failure to continue exercise. Muscle image used courtesy of https://www.aic.cuhk.edu.hk/web8/Muscle.htm.

limb exercising and inducing a hormonal increase,[60] and this lack of difference seems to suggest that the response is local to the exercising muscle rather than systemic. This may be due to the lack of exercise in the control limb, but when comparing walk training with and without blood flow restriction, there was no statistically significant correlation found between the acute hormonal response and the long-term increase in muscle size following blood flow restriction walk training only.[54] Further, a study designed to investigate the relationship of the systemic hormonal response and exercise training–induced adaptations in muscle size and strength found that this acute rise in hormones, including testosterone, which is known to be anabolic at supraphysiological levels,[61] does not mediate the exercise-induced change in muscle size and strength.[62] This suggests that the relatively short duration and low magnitude to which testosterone is elevated,[63] if at all,[37,64] following blood flow restriction exercise would not be expected to augment muscle growth over the mechanical stimulus itself.

Reactive Oxygen Species

The role of reactive oxygen species as a mechanism for muscle growth has been proposed by some[65]; the direct role of these byproducts remains unclear following blood flow restriction resistance training.[66] The increased production of reactive oxygen species could produce a detrimental effect through the signaling of inflammatory pathways such as NF-kappa B,[67] and may lead to muscle damage following traditional resistance training.[68] In contrast, some evidence suggests that without a transient exercise response of interleukin-6, hypertrophy is blunted, possibly through the lost ability to activate satellite cells.[69] This suggests that there may be a delicate balance between whether the oxidative stress response is positive or negative with respect to skeletal muscle health.[66] In addition, it should be appreciated that the role of reactive oxygen species is multifaceted, and they can potentially affect other tissues, such as the vascular system, by inducing angiogenesis.[70] Following blood flow restricted leg extensions with a low load, lipid peroxidase, a marker of oxidative stress, was not elevated over baseline within 2 hours or at a 24-hour time point following exercise.[71] When examining blood flow restriction applied alone, oxidative stress increases similarly to that of high-load exercise.[72] When combining restriction with high-load exercise, the response of reactive oxygen species may be further augmented, however, when applying it during low-load exercise, the rise in reactive oxygen species is attenuated compared with low-load exercise alone.[73] Considering those results, if reactive oxygen species were to augment muscle size and strength adaptations, applying blood flow restriction to a high-load exercise training condition would be expected to augment muscle growth. However, a study examining the responses to high-load training with and without blood flow restriction found no differences between conditions.[74]

Satellite Cells

Satellite cells are known to be required for muscle tissue regeneration,[75] but they may also be important for long-term skeletal muscle growth, as it has been proposed that myofiber growth must be accompanied by myonuclear addition to provide

sufficient genetic material, allowing for increased protein translation.[76] Since skeletal muscle fibers are postmitotic, new myonuclei must come from the activation and differentiation of satellite cells, which are located between the basal lamina and the muscle cell membrane.[77] The requirement of satellite cells for short-term muscle growth has been refuted in rodent models,[78] but they seem to be required for long-term hypertrophy.[79] In humans, increased satellite cell content has been shown to be associated with the degree of muscle fiber hypertrophy following a resistance training program,[80] with the magnitude of the hypertrophic response being greater in participants who have a greater satellite cell content.[81] Blood flow restriction training to failure has also been shown to increase the activation and proliferation of satellite cells, resulting in an addition of myonuclear content within both type I and type II muscle fibers.[82] In response to mechanical tension during exercise, a signaling cascade, mediated by nitric oxide synthase results in the release of hepatocyte growth factor from being bound to the muscle extracellular matrix,[83,84] which can bind to the c-Met receptor and activate the quiescent satellite cell.[85] Satellite cells have also been observed to be activated via whole-body vibration protocols when applying blood flow restriction.[86] This may be due to the restriction of blood flow creating a metabolic environment during vibration, which is augmenting the tension created in the muscle, as participants were asked to maintain a half squat position for a total of 12 minutes (3 sets of 4 minutes). The intramuscular pressure generated by the half squat in combination with blood flow restriction could have created a hypoxic-like environment, which has the potential to stimulate hypoxia-inducible factor 1[87] and its downstream signaling processes, such as vascular endothelial growth factor and nitric oxide synthase gene expression,[88] in turn causing the release of hepatocyte growth factor and activating satellite cells via the c-Met receptor. However, further work should be done to explicate this potential mechanism.

MECHANISMS OF STRENGTH

Blood flow restriction in combination with aerobic and resistance exercise has been shown to increase muscle size and strength. Although the changes in these 2 outcomes are often observed concurrently in response to resistance training, they are not necessarily causative of one another. For instance, a study comparing the effects of blood flow restriction training with various loads and pressures resulted in differential increases in muscle growth, but all low-load groups increased muscle strength to a similar magnitude regardless of the differences in muscle size.[89] Similarly, Dankel et al[90] found that daily testing of the 1RM for 3 weeks resulted in similar increases in muscle strength between both arms despite only 1 arm increasing muscle size from volume training, suggesting that separate mechanisms, aside from muscle growth, are responsible for the increased strength. Although unlikely since both arms were training, the crossover effect on strength could be seen as a limitation to this study. However, similar results have been observed following a between-subjects design that saw no differences in strength increases between a group practicing the 1RM test twice weekly or a group performing a traditional protocol of 8 to 12 RM for 4 sets.[91] Given this apparent dissociation, the strength changes in response to blood flow restriction training are most likely driven by something other than muscle growth. Despite this, most research focuses on the mechanisms of muscle growth following blood flow restriction exercise and very little research has been done investigating the mechanism inducing strength adaptations in response to blood flow restriction training. Brandner et al[92] has investigated the acute corticomotor excitability following blood flow restriction exercise and found that a continuous blood flow restriction protocol increased motor-evoked potential up to 1 hour following exercise. The authors suggest that a repetitive increase in excitability of central motor pathways could lead to long-term adaptations in which motor unit recruitment patterns could be altered following blood flow restriction training. This increased cortical excitement may be stimulated by type III and IV sensory fibers, which are sensitive to the metabolites accumulated during blood flow restriction.[2] These same sensory fibers also seem to play a meaningful role in reducing cortical inhibition following a traditional resistance training program.[93] Interestingly, a recent study found no change in spinal excitability following 4 weeks of unilateral isometric training at 25% of maximal force, despite both groups (low load alone and low load with blood flow restriction) increasing strength.[94] This observation is surprising, considering the attendant increase in strength of the contralateral limb seen in the blood flow restriction group. However, as the authors suggest, this finding may allude to blood flow restriction eliciting adaptations upstream of the spinal motor neurons that were assessed in the current study. Nonetheless, the exact mechanisms underlying neural adaptations following long-term blood flow restriction training remain unclear, and as such future studies should be designed to answer this complex question. Furthermore, even though muscle growth does not seem to cause the strength increases observed following blood flow restriction training, the potential role of peripheral mechanisms, at the local muscular level, should not be ruled out completely and should also be investigated.

THE METHODOLOGY OF BLOOD FLOW RESTRICTION APPLICATION

Restriction is applied via an external compressive device, such as elastic bands[21,95] or pneumatic cuffs[3,96] usually placed at the most proximal portion of the limbs. Currently, no standard exists regarding blood flow restriction application, but multiple variables such as cuff width, cuff type, and individual characteristics should be considered.[97] This is because the restrictive stimulus transmitted to the tissue underneath the cuff is influenced by each variable, and as such all should be accounted for to ensure the desired stimulus is being applied as well as to make methodology replicable. Arterial occlusion pressure (the inflation pressure of the cuff required for the cessation of blood flow) in the upper[98] and lower[99] body is dependent upon the width of the cuff; the cessation of blood flow occurs at a lower pressure when cuff width is increased. If the same pressure is applied to an individual using a wide and a narrow cuff, the wide cuff will restrict blood flow to a greater degree. Further, interindividual differences in resting arterial occlusion pressure within the same cuff are driven mainly by limb circumference, with larger limbs requiring a greater pressure to occlude blood flow,[98–100] which is why restriction pressures need to be individualized instead of applying a single arbitrary pressure to all participants. Doing so will help to ensure all participants receive a similar stimulus, while avoiding the unnecessary application of too high a pressure. A wide range of restriction (40% to 90% arterial occlusion pressure) pressures seem to be effective for increasing muscle size when exercising with 30% 1RM.[3] However, when applying a higher pressure the cardiovascular response to blood flow restriction exercise is increased,[101] and some concern has been expressed regarding the safety of participants.[102] If a higher pressure is unnecessary (potentially dependent on the load used), then applying a pressure at the lower end of the effective range could lessen the risk of an adverse cardiovascular response to blood

flow restriction exercise.[103] Cuff material may also need consideration, specifically in the upper body. Although elastic and nylon cuffs seem to apply a similar restriction stimulus in the lower body,[104] arterial occlusion pressure in the upper body is significantly different depending upon the type of cuff used.[105] It is unknown why there are differences in the upper body compared with the lower. This could be related to the constraints of the equipment used in the lower body investigation, where arterial occlusion could not be reached in some individuals, reducing the sample size. Regardless, if pressure is made relative to the cuff used for the exercise protocol, the stimulus seems to be similar between the 2 cuff types used.[104,105] In addition, when using an elastic cuff (eg, Kaatsu) to restrict blood flow, the application of the cuff alone places some pressure on the tissue underneath the cuff. This initial pressure should be considered, as it could influence the stimulus, even when the cuff is inflated to the same pressure.[106] Taken together, the best way to ensure that methodology is replicable, participant safety is maximized, and that each participant receives a similar stimulus is to make restriction pressure relative to the cuff being used for restriction and to the individual.

SUMMARY

Overall, blood flow restriction has been shown to be an effective modality to augment neuromuscular adaptations across a variety of populations and settings. It can be applied in the upper and lower body alone, with electrostimulation, with aerobic exercise, and with resistance exercise. Blood flow restriction seems to induce muscular adaptations through mechanisms such as muscle cell swelling, and metabolite-induced fatigue, both being shown to increase the cellular signaling response for protein synthesis. In addition, blood flow restriction seems to increase corticomotor excitability, influencing force capacity of the neuromuscular system, which may lead to long-term changes in recruitment patterns. The fact that blood flow restriction resistance training with low loads elicits muscle size and strength increases at lower levels of mechanical stress and exercise volumes makes it an attractive alternative to high-load resistance training. Still, application should be considered carefully to avoid unnecessarily high pressures and to ensure everyone is receiving a similar stimulus.

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Safety of Blood Flow Restricted Exercise in Hypertension: A Meta-Analysis and Systematic Review With Potential Applications in Orthopedic Care

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Summary: Blood flow restricted (BFR) exercise has recently been promoted in the United States as a novel method to restore skeletal muscle strength and hypertrophy in primarily athletic and healthy populations. A specialized tourniquet restricts blood flow after which brief and intermittent exercise is performed with low to moderate loads of resistance. A hypertensive blood pressure (BP) response during BFR exercise has been identified as a potential adverse effect, which may be particularly concerning for patients who are hypertensive. Because of the possibility that a substantial proportion of older adults undergoing orthopedic surgery may have hypertension as well as the possibility of a hypertensive BP response from BFR exercise, we performed a comprehensive search for studies examining the acute and chronic BP response to BFR exercise in hypertensive subjects resulting in 6 studies with which a meta-analysis and systematic review were performed. The meta-analysis results found nonsignificant, slight increases in systolic BP and diastolic BP. The results of the systematic review found that BFR exercise seems to be safe in patients with hypertension with no adverse events reported in the 86 patients who participated in the 6 reviewed studies. The cardiovascular response to BFR exercise seems to vary depending on the muscle group being exercised as well as the method of BFR, but, in general, these measures are greater during BFR exercise compared with non-BFR exercise.

Key Words: blood flow restriction—exercise—hypertension—orthopedicsmeta-analysis—systematic review.

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Blood flow restricted (BFR) exercise training, also known as Kaatsu Training, is a novel method to build skeletal muscle mass, strength, and endurance. This method of training utilizes a tourniquet to induce brief and intermittent blood flow restriction to an exercising limb, resulting in the accumulation of metabolites which promote muscle growth. Thus, BFR provides the benefits of high-intensity resistance exercise while performing low-intensity resistance exercise. Even very low level aerobic exercises such as walking, when combined with BFR, has demonstrated improved muscle strength, hypertrophy, and functional performance compared with walking without BFR.[1]

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The authors declare that they have nothing to disclose.

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Older adults (> 60 y) often have difficulty maintaining and developing muscle mass and strength,[2] and they have a greater risk of injury with high-intensity resistance exercise than younger individuals.[3] In addition, the rate and volume of joint replacement surgeries performed in older adults has dramatically increased over the last 15 years.[4] Furthermore, older patients undergoing total hip and knee arthroplasty are more likely to experience postoperative complications, admission to the ICU, discharge to a skilled care facility, and longer hospital length of stay.[5] One factor that is apparently responsible for poorer outcomes in older patients after such procedures is an acute and debilitating loss of muscle mass and strength. Resistance exercise has been suggested to reduce sarcopenia, but older adults are often unable to perform resistance exercise because of injuries.[6] By enhancing the restoration of muscle mass and strength with low-intensity exercise, BFR provides significant potential benefits for the older population, both preoperatively and postoperatively.[7]

Although BFR is accepted as a safe training method for healthy populations, less is known about the safety of BFR in older adults and, specifically, for individuals with hypertension (HTN).[8] One in every 3 Americans suffers from HTN, with 1 in every 5 having undiagnosed and/or untreated HTN.[9,10] In older adults, the prevalence of HTN is an alarming 65%.[10] Thus, the probability of HTN in an older patient undergoing an orthopedic procedure is high. During all forms of exercise, the exercise pressor reflex results in an increase in mean arterial pressure. Some authors have expressed concern that BFR may exacerbate this hypertensive response and thus, be unsafe for individuals with HTN.[11] However, BFR at low loads has demonstrated reduced blood pressure (BP) and improved vascular compliance compared with the same low load training without restriction.[12–14]

It seems that systemic reductions in BP after performing BFR with low-level exercise may be related to a decrease in peripheral artery vascular resistance and improved endothelial function.[15] In addition, BFR has been shown to increase vascular endothelial growth factor (VEGF)—a potent stimulus of angiogenesis.[16] Furthermore, one study of BFR exercise in healthy adults found that BFR elicited a cardiovascular response similar to standing without detrimental effects on cardiovascular function.[17] The purposes of this paper are to provide a (1) cursory overview of the effects of BFR exercise on vascular and cardiovascular function, and (2) meta-analysis and systematic review of BFR exercise in HTN.

EFFECT OF BFR EXERCISE ON VASCULAR AND CARDIOVASCULAR FUNCTION

The effect of BFR exercise on vascular function in healthy subjects has demonstrated conflicting results. Some studies

show improvements in vascular function, whereas others demonstrate no substantial change.[18] At the very least, it does not seem that BFR exercise impairs vascular function in healthy subjects. The inconclusive effects of BFR exercise on vascular function may be because of a variety of factors including the age and sex of the subjects, the muscle group undergoing BFR exercise, the manner by which BFR exercise is employed (ie, method, duration, and repetitions of BFR exercise), and the outcome measures used to examine vascular function.[18] Each of the above factors may be partly responsible for the inconclusive effects of BFR exercise on vascular function. Nonetheless, Figure 1 shows the manner by which BFR exercise is likely to impact vascular function, skeletal muscle strength, and skeletal muscle hypertrophy. The major factors responsible for improved vascular function seem to be increased VEGF with subsequent angiogenesis as well as improved endothelial function.[19–21]

Although the effect of BFR exercise on vascular function is not completely understood, one potentially beneficial mechanism for subjects with HTN is postexercise induced hypotension.[22–25] The only study which has examined the effects of BFR exercise on postexercise BP found that an acute bout of BFR exercise in 10 young healthy men, performed at 20% of 1 repetition maximum (1-RM), produced a nonsignificant reduction in BP postexercise. However, the same study found that high intensity resistance exercise at 70% 1-RM without BFR produced a significant decrease in postexercise systolic BP at 60 minutes postexercise.[25] Despite these findings, it is important to note that postexercise hypotension is much more profound in subjects who are hypertensive.[22–25] Perhaps this is why a study examining individual changes in resting BP in response to BFR exercise and resistance training found that BP adaptation to resistance training and exercise with BFR was not homogeneous.[24] Nonetheless, further investigation of BFR exercise on BP and postexercise BP in healthy subjects and subjects with HTN warrants further investigation.

Because a substantial proportion of older adults undergoing orthopedic procedures are likely to have HTN and BFR exercise seems to be an emerging method to improve skeletal muscle strength, hypertrophy, and function, we performed a comprehensive search for studies examining the acute and chronic BP response to BFR exercise in hypertensive subjects. The search identified 6 studies with which a meta-analysis and systematic review were performed.

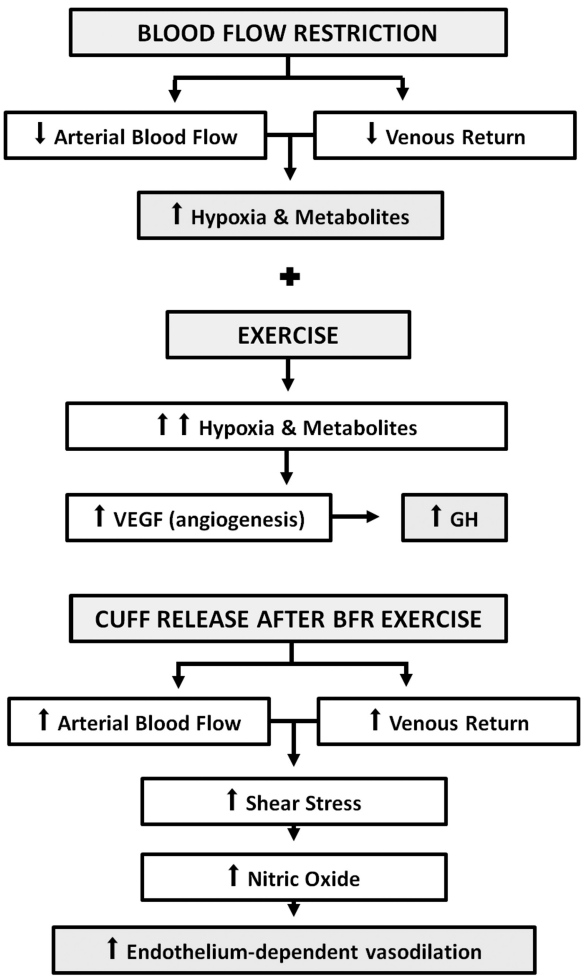

FIGURE 1. Potential effects of blood flow restricted exercise and mechanisms of action. GH indicates growth hormone; VEGF, vascular endothelial growth factor. full color online

META-ANALYSIS AND SYSTEMATIC REVIEW OF BFR EXERCISE IN HTN

Meta-analysis Methods

A literature search was performed in PubMed and the Cochrane library through October 2016. The search strategy was conducted in English and Portuguese and included a mix of terms for the key concepts Blood Flow Restriction, KAATSU, Training, Exercise, Cardiovascular Disease, Heart Disease, Hypertension, and these were later combined with an advanced search strategy to identify randomized controlled trials for inclusion purposes. The reference list of eligible studies was also screened to identify other potentially relevant papers.

To be included in this meta-analysis, a study had to meet the following criteria: (a) the study was conducted in hypertensive humans in whom other concomitant diseases were reasonably well excluded, (b) there was random allocation of study participants to training and control groups, (c) the use of BFR was the sole intervention difference with the control group. Any studies not meeting these criteria were excluded. Three studies were eventually included in this meta-analysis (Table 1).[26–28] The detailed process of the literature search is presented in Figure 2.

Each study was read and coded independently by 2 authors for descriptive information including: (a) publication year, (b) source of publication (ie, journal article or unpublished dissertations and theses), (c) sex (1 = only males; 2 = only females; 3 = mixed), and (d) age of the samples. For both BFR and standard training protocols, we coded for type and frequency of exercise. Type of exercise was coded based on what extremities were used during the training: 1 = upper body only; 2 = lower body only; or 3 = both upper and lower bodies. Frequency was coded by the total number of sessions performed throughout the studies. Means and SD deviations of both systolic blood pressures (SBPs) and diastolic blood pressures (DBPs) were recorded as continuous variables in millimeters of mercury (mm Hg). Means and SD of heart rate (HR) were also recorded as continuous variables and measured in beats per minute (bpm). Interrater reliability was calculated for all continuous and categorical variables. Cohen's κ determined that the raters were in complete agreement (k = 1). Pearson

TABLE 1. Studies of BFR Exercise in Hypertension Included in the Meta-Analysis

Reference	Sample Size/Inclusion Criteria/Meds	Outcome Measures	Procedures Employed	Results
Araujo et al[26]	Fourteen women (mean ± SD age of 45 ± 9.9 y). Inclusion was limited to nonsmokers aged 60 and younger who had been diagnosed with hypertension type 1 (WHO/ISH, 1999). No medications were reported, but subjects were instructed to avoid medications on test days	HR, SBP, DBP, BMI, % G, MM, HWR, 1-RM	Acute and chronic assessment of HR and BP before the start of the test, immediately after the first, second and third sets, and 15, 30, 45, and 60 min after each exercise session. Two sessions (3 sets of 15 repetitions each) of bilateral knee extension with some differences between groups were carried out. For the BFR group, the subjects performed bilateral knee extension at 30% 1-RM with a sphygmomanometer applied around the upper thigh of each leg (80% arterial occlusion pressure), with a load of 30% of a maximum repetition and a rest period of 45 s between sets. For the control group, the load used during the test was 80% of a maximum repetition, without arterial occlusion and with rest periods of 1 min between sets	No adverse events were reported. SBP decreased at all time points (15, 30, 45, and 60 min) after BFR training. HR increased from the first to the third set in all groups. A significant increase in DBP was observed from the first to the second set in the BFR group, followed by a reduction of DBP between the second and third sets
Cezar et al[27]	Eight women in the BFR group (mean ± SD age of 63.75 ± 11.58 y), 8 women in the control group (mean ± SD age of 59 ± 13.03 y) with a resting BP <160/105 mm Hg and BMI < 35 kg/m². All subjects underwent antihypertensive therapy which was maintained throughout the study, but the specific antihypertensive medications were not named	HR, SBP, DBP, MAP, DP, CORT, IL-6, BMI, 1-RM	Chronic study in which all data were collected 48 h before initiation of the exercise program, and 48 h after the end of the last training session. HR and BP were measured before each training session after the subjects remained at rest for 10-12 min. All the BFR group performed wrist flexion exercise with vascular occlusion (70% of SBP) implemented on the medial portion of both arms using sphygmomanometers. Each subject performed 3 sets with loads corresponding to 30% of their 1-RM strength at intervals of 30-s between sets. The control group followed the same wrist flexion exercise protocol as the WFBFR group, except that the load used was 80% of subject 1-RM strength and without vascular occlusion	No adverse events were reported. Eight weeks of wrist flexion exercise with BFR were efficient to produce a significant reduction in SBP, DBP, MAP, and DP from pretest to posttest. However, BFR training did not produce significant changes in CORT or IL-6 concentrations
Bonorino et al[28]	Seven women in the BFR group (mean ± SD age of 68.13 ± 4.43 y), 7 women in the control group (mean ± SD age of 69.14 ± 7 y) who were participants of a strength training program for at least 3 months. All subjects underwent antihypertensive therapy which was maintained throughout the study and similar amounts were administered between the 2 groups, but the specific antihypertensive medications were not named. Also, no hypertensive inclusion or exclusion criteria were reported	HR, SBP, DBP, 1-RM	Acute assessment of BFR was used as an additional intervention (preworkout). Treatment group performed the "preworkout" (wrist flexion with BFR at 30% 1-RM, 70% occlusion pressure) before a standard strength training without BFR. The control group underwent no "preworkout" at all, but performed resistance training without BFR at 70%-80% 1-RM. All measures were taken at rest, immediately after BFR "preworkout" and poststandard strength training	No adverse events were reported. No differences in HR were observed between groups. Reductions in both SBP and DBP were observed in the treatment group, whereas the control group only elicited a reduction in DBP. Both the training and control groups improved 1-RM

1-RM indicates 1 repetition maximum; BFR, blood flow restricted; BMI, body mass index; BP, blood pressure; CORT, cortisol; DBP, diastolic blood pressure; DP, double product; HR, heart rate; HWR, hip-waist ratio; IL-6, interleukin-6; MAP, mean arterial pressure; MM, muscle mass; SBP, systolic blood pressure; WFBFR, wrist flexion exercise with blood flow restriction; %G, fat-free mass.

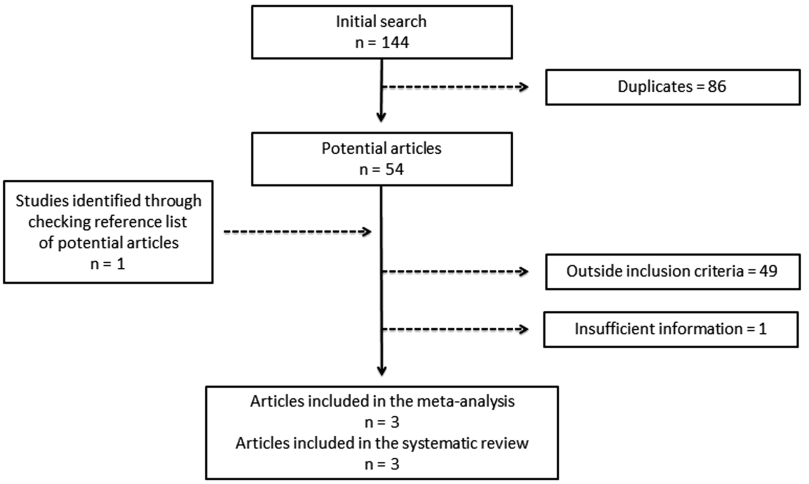

FIGURE 2. Meta-analysis and systematic review of blood flow restriction exercise in hypertension study selection flow chart.

correlation analysis also demonstrated complete consistency among coders (r = 1).

Data analyses included calculation of the standardized mean difference effect sizes (d, ES) for SBP, DBP, and HR values of treatment versus control postintervention data. The standardized mean difference quantifies the mean difference on dependent variable between treatment and control groups in SD unit. The overall effect was computed from effect sizes extracted from the individual studies, each of which was weighted by its inverse of the associated variance. Heterogeneity of effect sizes was examined using the Q statistic. The Q statistic is the weighted sum of squares produced by determining and squaring the deviation of each study's ES from the mean ES, multiplying by each study's inverse of the variance, and summing the values. As such, the Q statistic is a standardized measure of the total amount of variation observed across studies. This value may be compared with the amount of expected variation because of within-study differences, expressed as degrees of freedom (df). The amount of heterogeneity of ES because of between-study differences is determined by subtracting expected variation (df) from the observed variation (Q). Effect sizes were synthesized using either fixed-effects or random-effects models and presented with 95% confidence intervals (CIs) and *P*-values. Statistical significance was set at a *P*-value <0.05. All analyses were performed using R Statistical Software (available from: http://www.r-project.org) with a meta-analysis package named metaphor.

Meta-analysis Results

The 3 trials that were reviewed included 2 published articles and 1 thesis (Table 1).[26–28] The methodological quality of the studies using the PEDro scale was moderate with 2 studies scoring a 5 of 10,[26,28] and 1 study scoring 6 of 10 (Table 2).[27] Two studies were used to examine the acute effects of BFR exercise immediately after a single BFR exercise bout,[26,28] and all 3 were used to examine the chronic effects of BFR exercise.[26–28] The trials were all conducted in Brazil between 2014 and 2016 and were of randomized design with a BFR training group and a training control group with no vascular occlusion. The included studies evaluated a total of 44 hypertensive subjects, all of them female, with a mean sample size of 14.67 (SD = 1.155). The mean age across studies ranged from 45.71 to 68.13 years.[26–28] Inclusion criteria for BP was 1999 World Health Organization Type 1 HTN (< 160/100 mm Hg),[26] <160/105 mm Hg in another study,[27] and no criteria were listed for the other study.[28] None of the studies reported which specific antihypertensive medications were administered to the study subjects, but 1 study instructed patients to avoid medications on the test days,[26] whereas another indicated that a similar amount of antihypertensive medications were administered to both the experimental and control groups.[28]

Each of the studies reported that no adverse events were observed during or after the study period.[26–28] One of the studies applied BFR using sphygmomanometer cuffs placed around the proximal thighs bilaterally at 80% arterial occlusion pressure and had subjects perform knee extension exercise at 30% of 1-RM and compared responses to non-BFR knee extension performed at 80% 1-RM.[26] The other 2 studies applied BFR using sphygmomanometer cuffs placed around the proximal portion of the arms bilaterally at 70% arterial occlusion pressure and performed bilateral wrist flexion at 30% of 1-RM and compared responses to non-BFR wrist flexion

TABLE 2. Methodological Quality of the Included Studies Assessed With the PEDro Scale

PEDro*	Araujo et al[26]	Cezar et al[27]	Bonorino et al[28]
Eligibility criteria	Yes	Yes	Yes
Randomized allocation	Yes	Yes	Yes
Concealed allocation	No	Yes	No
Groups similar at baseline	Yes	Yes	Yes
Blind subjects	No	No	No
Blind therapists	No	No	No
Blind assessors	No	No	No
Measure of one key outcome obtained from > 85% initial subjects	Yes	Yes	Yes
Intention-to-treat	No	No	No
Between-group comparisons	Yes	Yes	Yes
Point measures and measures of variability	Yes	Yes	Yes
TOTAL	5/10	6/10	5/10

*Eligibility criteria is not used to calculate the PEDro score.

performed at 70% to 80% 1-RM.[27,28] We computed standardized mean difference effect sizes (d, ES) for SBP, DBP, and HR values of treatment versus control immediately postintervention (to measure the acute effects of BFR exercise) and after the intervention (to measure the chronic effects of BFR exercise which included hours to days postintervention) for each study. Risk of publication bias could not be assessed because of the low number of included studies. The meta-analysis results of the acute and chronic effects of BFR exercise on SBP, DBP, and HR are shown in Figure 3.

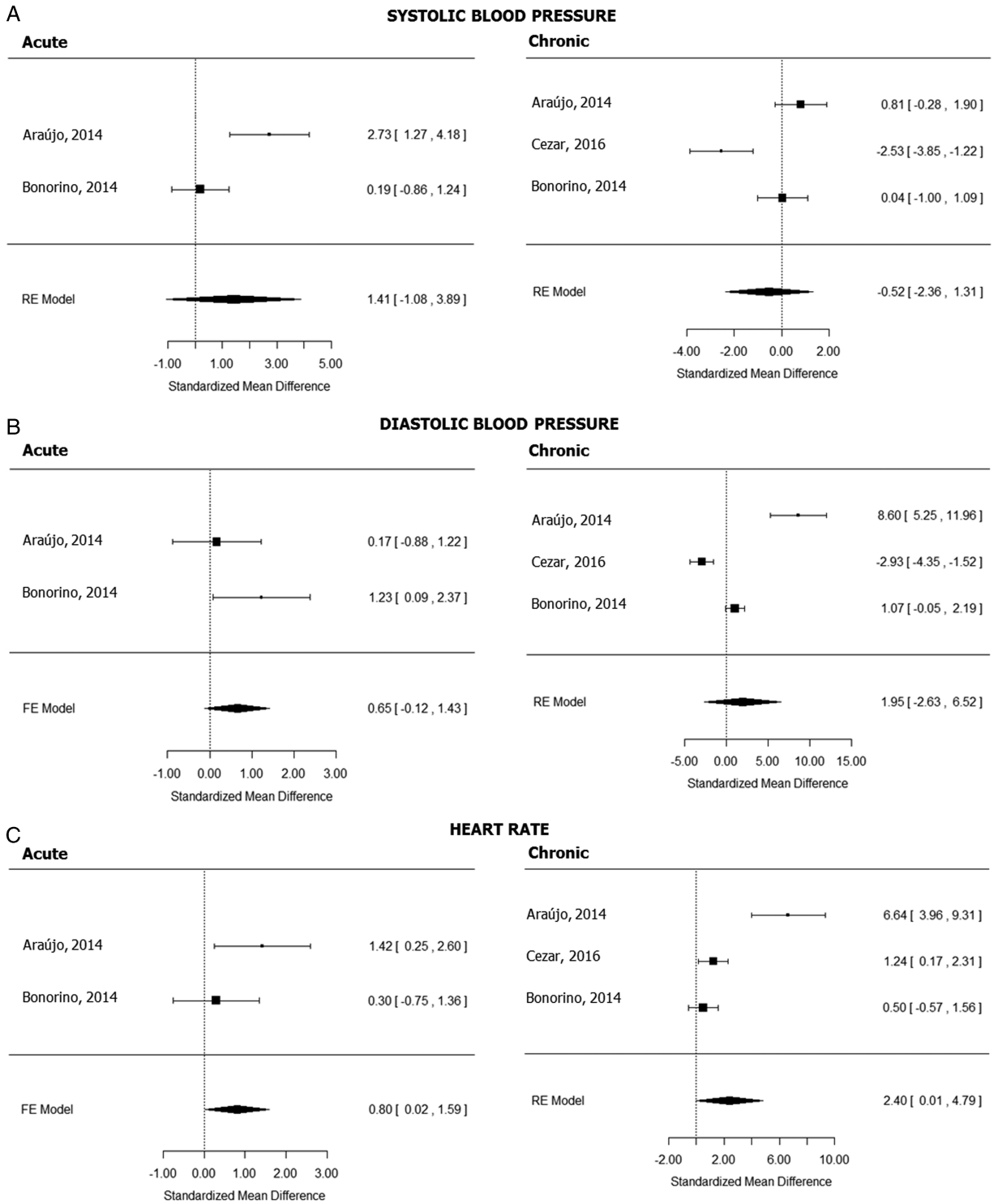

FIGURE 3. Meta-analysis results of the acute and chronic effects of blood flow restriction exercise on (A) systolic blood pressure, (B) diastolic blood pressure, and (C) heart rate.

ACUTE AND CHRONIC EFFECTS OF BFR EXERCISE ON SBP

Acute Effect

A test for heterogeneity was performed to check whether between-study variance existed. A significant Q-statistics of 7.66 ($P < 0.005$) with 1 degree of freedom indicated that between-study variance existed. Therefore, the overall effect was estimated under a random-effects model, where between-study variation estimated using the DerSimonian and Laird (DL) method was incorporated into each effect. The estimated between-study variance using DL was 2.79. The computed I-squared value of 0.86 suggests a large magnitude of between-study variance in effects.

The estimated average effect was 1.41 with a standard error of 1.266, which was not found to be statistically significant ($z = 1.11$; $P = 0.26$; 95% CI, −1.08 to 3.89) suggesting that BFR exercise has no significant effect on SBP immediately after training.

Chronic Effect

A significant Q-statistics of 15.45 ($P < 0.001$) with 2 degrees of freedom indicated that between-study variance existed. Therefore, a random-effects model was used to calculate the overall effect which was computed by incorporating between-study variance using the DL method. The estimated between-study variance using the DL method was 2.29. The computed I-squared value of 0.87 suggests a large magnitude of between-study variance in effects.

The estimated average effect was −0.52 with a standard error of 0.93, which was not found to be statistically significant ($z = -0.55$; $P = 0.57$; 95% CI, −2.36 to 1.31) suggesting that BFR exercise has no significant effect on SBP chronically.

ACUTE AND CHRONIC EFFECTS OF BFR EXERCISE ON DBP

Acute Effect

A nonsignificant Q-statistics of 1.796 ($P = 0.18$) suggested that between-study variance did not exist. Thus, a fixed-effects model was used revealing that the estimated common standardized mean difference was 0.65 with a standard error of 0.39, which was not found to be statistically significant (z, 1.66; *P*, 0.09, 95% CI, −0.12 to 1.43) suggesting that BFR exercise has no significant effect on DBP immediately after training.

Chronic Effect

A significant Q-statistics of 45.28 ($P < 0.0001$) with 2 degrees of freedom indicated that between-study variance existed. Therefore, a random-effects model was used to calculate the overall effect which was computed by incorporating between-study variance using the DL method. The estimated between-study variance using the DL method was 15.17. The computed I-squared value of 0.95 suggests a large magnitude of between-study variance in effects.

The estimated average effect was 1.95 with a standard error of 2.33, which was not found to be statistically significant (z, −0.83; *P*, 0.40; 95% CI, −2.63 and 6.52) suggesting that BFR exercise has no significant effect on DBP chronically.

ACUTE AND CHRONIC EFFECTS OF BFR EXERCISE ON HR

Acute Effect

A nonsignificant Q-statistics of 1.94 ($P = 0.16$) suggested that between-study variance did not exist. Thus, a fixed-effects model was used revealing that the estimated common standardized mean difference was 0.80 with a standard error of 0.39, which was found to be statistically significant (z, 2.00; *P*, 0.04; 95% CI, 0.02 and 1.59) suggesting that BFR exercise has a significant effect on HR immediately after training.

Chronic Effect

A significant Q-statistic of 17.52 ($P < 0.001$) with 2 degrees of freedom indicated that between-study variance existed. Therefore, a random-effects model was used to calculate the overall effect, which was computed by incorporating between-study variance via the DL method. The estimated between-study variance using the DL method was 3.76. The computed I-squared value of 0.88 suggests a large magnitude of between-study variance in effects.

The estimated average effect was 2.4 with a standard error of 1.22, which was found to be statistically significant (z, −1.96; *P*, 0.04; 95% CI, 0.01 and 4.79) suggesting that BFR exercise has a significant chronic effect on HR.

Discussion of the Meta-Analysis Results

The results of the meta-analysis presented above suggest that BFR elicits a nonsignificant acute and chronic effect on SBP and DBP, but significant effect on HR. The acute effect of BFR exercise on SBP appears to be a slight increase, whereas the chronic effect of BFR exercise on SBP seems to be a slight decrease. The acute and chronic effect of BFR exercise on DBP seems to be a slight increase. The acute and chronic effect of BFR exercise on HR seems to be a significant increase.

The above findings suggest that BFR exercise elicits minor effects on BP in hypertensive subjects both acutely and chronically, which may in part be because of antihypertensive medications or the methods of BFR implemented in the studies. The relatively high degree of between-study variance may also be partly responsible for the above findings. In addition, the studies used in this meta-analysis were performed only in women limiting the generalizability of the results.[26–28] Thus, further investigation of the effects of BFR exercise in hypertensive men and women is warranted, but the finding that no adverse events occurred during BFR exercise in the above studies is encouraging.

Systematic Review of BFR Exercise in HTN

Table 3 shows 3 additional studies of BFR exercise performed in hypertensive subjects that did not meet the inclusion criteria for the above meta-analysis because of the lack of a control group.[15,29,30] The acquisition of the studies and methods used to extract data was identical to the process described for the meta-analysis above. A total of 42 hypertensive patients were included in this systematic review of whom the majority were older women.[15,29,30] Inclusion criteria for BP was <160/100 mm Hg in 2 of the studies and <170/100 mm Hg in the other study. One study did not report on antihypertensive medication use, but 2 of the studies by the same investigator reported that subjects were administered Angiotension II receptor antagonists and Angiotension converting enzyme inhibitor antihypertensive agents.[15,29,30]

TABLE 3. Studies of BFR Exercise in Hypertension Included in the Systematic Review

Reference	Sample Size/Inclusion Criteria/Meds	Outcome Measures	Procedures Employed	Results
Satoh[15]	Eighteen subjects (7 males, 11 females; age range from 30-90 y) with a resting BP < 170/100 mm Hg. No medications were reported	SBP & DBP as well as HbA1c, LDL-cholesterol, weight, and BMI	Three to 4 mo of BFR Ex (using Kaatsu belts and Training Device) in either the arms or legs performed for 6-12 min, 1-2×/week, at a Borg RPE of 13 and at 60-160 mm Hg for the UE and 80-200 mm Hg for the LE during 3 bilateral exercises (finger and toe flexion and extension; shoulder flexion and extension and toe raise and descend; and elbow extension with calf raises) separated by 20 s rest periods	No adverse events were reported. SBP decreased 12 ± 2.9%, DBP decreased 10 ± 2.2%. BFR Ex also decreased HbA1c 10 ± 0.6%, LDL-chol 14 ± 2.6%, body weight 12 ± 1.9%, and BMI 12 ± 0.5%
Pinto et al[29]	Eighteen women (mean ± SD age of 67 ± 2 y) with a resting BP < 160/100 mm Hg. 12 subjects were administered Angiotension II receptor antagonists and 6 subjects were administered Angiotension converting enzyme inhibitor antihypertensive agents	HR, SBP, DBP, SV, CO, SVR, blood lactate, Borg RPE	Acute assessment of HR, SBP, DBP, SV, CO during bilateral knee extension at 65% 1-RM without BFR consisting of 3 sets of 10 reps separated by 60 s rest periods compared with bilateral knee extension at 20% of 1-RM with BFR Ex (80% arterial occlusion pressure below the inguinal fold bilaterally using a blood pressure cuff with a width of 18 cm and length of 90 cm) consisting of 3 sets of 10 reps separated by 60 s rest periods during which the 80% arterial occlusion pressure was maintained. A resting assessment of the effects of BFR without exercise was also performed during which HR, SBP, DBP, SV, CO, SVR were also examined. The HR, SBP, DBP, SV, CO, SVR were examined at rest, immediately after each of the 3 reps, during each 60 s rest period, and 5 min after the third rep	No adverse events were reported. BFR with Ex produced a significantly greater HR, SBP, DBP, SVR from the first to third set without significant effect on SV, but with a significant increase in CO after the first set. The increase in HR, SBP, DBP were similar between BFR ex at 20% of 1-RM and 65% 1-RM without BFR. All measurements except for SVR were significantly lower 5 min after completing the 3 sets for both BFR Ex and non-BFR Ex. The measurements during the rest periods between BFR exercise sets revealed significantly greater SBP, DBP, and SVR compared with preexercise and compared with the rest period after the first rep, but with significantly lower SV and CO at the same time periods. Blood lactate levels and Borg RPE were significantly greater with knee extension at 65% 1-RM without BFR compared with BFR Ex
Pinto and Polito[30]	Twelve women (mean ± SD age of 57 ± 7 y) with a resting BP < 160/100 mm Hg. Eight subjects were administered Angiotension II receptor antagonists and 4 subjects were administered Angiotension converting enzyme inhibitor antihypertensive agents	HR, SBP, DBP, SV, CO, SVR, Borg RPE	Acute assessment of HR, SBP, DBP, SV, CO during bilateral leg press exercise at 65% 1-RM without BFR consisting of 3 sets of 15 reps separated by 60 s rest periods compared with bilateral leg press exercise at 20% of 1-RM with BFR Ex (80% arterial occlusion pressure below the inguinal fold bilaterally using a blood pressure cuff with a width of 18 cm and length of 70 cm) consisting of 3 sets of 8 reps separated by 60 s rest periods during which the 80% arterial occlusion pressure was maintained which was compared with bilateral leg press exercise at 20% of 1-RM without BFR consisting of 3 sets of 15 reps separated by 60 s rest periods. The HR, SBP, DBP, SV, CO, SVR were examined at rest, immediately after each of the 3 reps, during each 60 s rest period, and approximately 5 min after the third rep	No adverse events were reported. BFR with Ex produced a significantly greater HR, SBP, DBP, SVR from the first to third set which were significantly greater than the HR, SBP, DBP, SVR during Ex. at 65% 1-RM without BFR Ex. No significant effect on SV was observed during an Ex. conditions. The measurements during the rest periods between BFR exercise sets revealed significantly greater HR, SBP, DBP, and SVR compared with Ex. at 65% 1-RM without BFR Ex. Borg RPE was significantly greater with BFR Ex. compared with Ex. at 65% 1-RM

1-RM indicates 1 repetition maximum; BFR, blood flow restricted; BMI, body mass index; BP, blood pressure; CO, cardiac output; DBP, diastolic blood pressure; Ex, exercise; HR, heart rate; LDL=low-density lipoprotein; LE, lower extremities; RPE, rate of perceived exertion; SBP, systolic blood pressure; SV, stroke volume; SVR, systemic vascular resistance; UE, upper extremities.

The studies presented in Table 3 also reported that no adverse events were observed during BFR exercise.[15,29,30] One of the studies examined the chronic effects of BFR exercise (bilateral upper or lower extremity exercise for 3 to 4 mo) on BP,[15] and the other 2 studies examined the acute effects of BFR exercise (bilateral knee extension in one study and bilateral leg press in the other) on BP.[29,30] The chronic study used Kaatsu belts and training device[15] whereas the 2 acute studies used BP cuffs with a width of 18 cm and length of 70 to 90 cm to elicit BFR.[29,30] The bilateral knee extension and leg press studies applied 80% arterial occlusion pressure below the inguinal fold bilaterally while performing 3 sets of 10 reps at 20% 1-RM separated by 60 second rest periods.[29,30] Both of the acute studies compared BFR exercise at 20% 1-RM to non-BFR exercise at 65% 1-RM.[29,30] The chronic study of BFR using Kaatsu belts applied a pressure of 60 to 160 mm Hg for the upper extremity and 80 to 200 mm Hg for the lower extremity to elicit BFR while performing 3 bilateral exercises for 6 to 12 minutes separated by 20 second rests, 1 to 2×/week, and at a Borg RPE of 13.[15] The BFR was maintained during the rest periods in each of the 3 studies (Table 3).[15,29,30]

The chronic effect of BFR exercise on BP was substantial with a 12% and 10% reduction in SBP and DBP, respectively. Improvements in body weight, body mass index, cholesterol, and hemoglobin A1C were also observed after BFR exercise was performed chronically (Table 3).[15] The acute effect of BFR exercise observed in the 2 acute BFR exercise studies was slightly different and likely because of the exercise being performed and the muscles performing the exercise since the studies were performed by the same investigators using the same methodology.[29,30] The acute effect of BFR knee extension at 20% 1-RM produced a significantly greater HR, SBP, DBP, and systemic vascular resistance (SVR) from the first to third set which were similar to the response observed during knee extension at 65% 1-RM.[29] The measurements during the rest periods between BFR knee extension sets revealed a significantly greater SBP, DBP, and SVR compared with the rest periods between knee extension sets at 65% 1-RM without BFR.[29] All measurements except for SVR were significantly lower 5 minutes after completing the 3 knee extension sets for both BFR exercise and non-BFR exercise (Table 3).[29]

In the other acute BFR exercise study, BFR leg press exercise also produced a significantly greater HR, SBP, DBP, and SVR from the first to third set which were significantly greater than the HR, SBP, DBP, and SVR during leg press exercise at 65% 1-RM without BFR.[30] The measurements during the rest periods between BFR leg press sets revealed significantly greater HR, SBP, DBP, and SVR compared with the rest periods between leg press exercise sets at 65% 1-RM without BFR (Table 3).[30] No significant difference in stroke volume (SV) was observed during the rest periods or during the leg press BFR exercise when compared with leg press exercise at 65% 1-RM without BFR, but the cardiac output (CO) was significantly lower during rest periods and during leg press BFR exercise compared with leg press exercise at 65% 1-RM.[30] Of note, is that the SV and CO were similar during BFR knee extension and knee extension at 65% 1-RM, but both SV and CO were significantly lower during the rest periods after BFR knee extension compared with knee extension at 65% 1-RM.[30] The Borg RPE was significantly greater with BFR leg press exercise compared with leg press exercise at 65% 1-RM without BFR,[30] but was significantly greater during knee extension exercise at 65% 1-RM compared with BFR knee extension (Table 3).[30]

In view of the above results BFR exercise seems to have a beneficial chronic effect on lowering both SBP and DBP.[15] However, the exercise performed and muscle group performing exercise during BFR seem to affect the cardiovascular response.[29,30] The larger muscle mass performing leg press exercise with BFR produced a significantly greater cardiovascular response compared with leg press exercise performed at 65% 1-RM without BFR,[30] but the smaller muscle mass performing knee extension elicited a cardiovascular response that was similar between BFR and non-BFR knee extension.[29] The HR, SBP, DBP, and SVR during the rest periods between BFR exercise sets was significantly greater compared with non-BFR exercise and was similar in both acute BFR exercise studies.[29,30] The SV and CO findings during BFR exercise and during the rest periods were mostly similar to non-BFR exercise and the lower CO during BFR leg press compared with non-BFR leg press is likely because of the larger muscle mass recruited to perform the leg press compared with knee extension since greater blood flow is required to perform the leg press which subsequently decreased venous return because of BFR and produced a lower CO.[29,30] Furthermore, leg press exercise may compress the vasculature within the legs to a greater degree and subsequently decrease venous return even more leading to a lower CO.[30] The results of the above studies highlight the need to carefully consider the muscle group when performing exercise with BFR.[29,30]

BFR EXERCISE SEEMS TO BE SAFE IN PATIENTS WITH HTN AND BENEFICIAL FOR PATIENTS WITH ORTHOPEDIC DISORDERS

The above results indicate that BFR exercise seems to be safe in patients with HTN in view of the available literature.[13,15,26–32] No adverse events have been reported in the 6 studies presented above, representing a total of 86 patients.[13,15,26–32] The SBP, DBP, and HR response seems to vary depending on the muscle group being exercised as well as the method of BFR, but in general these measures are greater during BFR exercise compared with non-BFR exercise.[13,15,26–32] The results of the meta-analysis suggest that BFR elicits a nonsignificant acute and chronic effect on SBP and DBP, but significant effect on HR.[26–28] The acute effect of BFR exercise on SBP seems to be a slight increase whereas the chronic effect of BFR exercise on SBP seems to be a slight decrease. The acute and chronic effect of BFR exercise on DBP seems to be a slight increase. The acute and chronic effect of BFR exercise on HR seems to be a significant increase.[26–28]

The effects of BFR exercise presented in the above systematic review support the clinical application of BFR exercise in older and younger patients with orthopedic disorders despite being hypertensive. Furthermore, there seems to be substantial potential for preoperative and postoperative BFR exercise to attenuate sarcopenia. Finally, BFR exercise provided preoperatively has the potential to elicit skeletal muscle hypertrophy and strength which is likely to facilitate favorable postoperative outcomes such as fewer postoperative complications and discharges to skilled care facilities as well as possibly reducing hospital length of stay.[5] Future investigation of BFR exercise in patients undergoing orthopedic procedures, both preoperatively and postoperatively, is warranted.

SUMMARY

The results of this meta-analysis and systematic review found that BFR exercise in hypertensive subjects was performed safely and produced nonsignificant, slight increases in SBP and DBP. The cardiovascular response to BFR exercise

seems to vary depending on the muscle group being exercised as well as the method of BFR exercise with BFR exercise eliciting a greater cardiovascular response than non-BFR exercise. In view of the above findings, BFR exercise seems to be a safe and effective intervention in patients with HTN in need of skeletal muscle strengthening and hypertrophy before, after, or both before and after an orthopedic procedure.

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Blood Flow Restriction Therapy for Stimulating Skeletal Muscle Growth: Practical Considerations for Maximizing Recovery in Clinical Rehabilitation Settings

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Summary: Inactivity following injury and surgery due to pain, instability, or immobilization results in loss of muscle mass and function. As a result, both risk of reinjury and overall recovery time are a prime concern for clinicians and therapists trying to minimize these deleterious effects. While resistance exercise has been demonstrated to be highly effective in combating loss of muscle mass and function, it is often not advised for postoperative or injured patients because of elevated risk of injury or exacerbating existing injury sites. Low-intensity resistance exercise (< 30% 1 repetition-maximum) performed with mild to moderate blood flow restriction (BFR) has been observed to elicit beneficial anabolic and functional responses in skeletal muscle that are governed by mechanisms that regulate muscle protein metabolism and myogenesis similar to the responses following high-intensity resistance exercise. On the basis of these findings, practical applications of BFR in clinical and sport settings have been developed to mitigate skeletal muscle loss following injury and accelerate rehabilitation. However, many aspects of the physiological effects of BFR therapy in rehabilitation settings remain unclear. This review provides current information regarding skeletal muscle responses to BFR with a focus on skeletal muscle protein metabolism, anabolic signaling, applied outcomes, and applications in the clinical setting.

Key Words: BFR—occlusion—KAATSU—resistance exercise—rehabilitation.

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Blood flow restriction (BFR) therapy utilizes a specialized automated pressure cuff that is applied around the thigh or upper arm, and restricts vascular flow by direct compression of the limb when activated.[1] Modified from a popularized form of resistance training referred to as "Kaastu Training," therapies using this procedure have been shown to acutely stimulate muscle growth (through mechanisms yet to be determined).[1] When combined with low-intensity exercise (LIX), performed at intensities below 30% of maximal strength, BFR has been shown to improve fatigue resistance and produce increases in strength that are reportedly comparable to high-intensity resistance exercise (HIX) in general population subjects and in athletes.[2–4] Thus, this type of intervention may be promising for patients with joint injuries during postoperative recovery and rehabilitation.

While several investigations indicate that BFR may assist in eliciting an anabolic response in isolation or when combined with resistance exercise (BFR-LIX), the mechanisms by which BFR therapy may act on skeletal muscle to prevent atrophy and preserve function remain an ongoing research focus. Continued acute and chronic BFR investigations are needed for (1) greater understanding of the underlying mechanism that govern physiological responses to BFR therapy, (2) refinement of current BFR treatment protocols, (3) better identification of patients who may benefit from such therapies, (4) and for further development of standards and expectations by which physical therapists (PT) may set rehabilitation goals and milestones in the clinical setting.

THE CASE FOR STIMULATION OF MUSCLE GROWTH WITH ACUTE AND CHRONIC BFR

Several studies in recent years have provided a great deal of information in an attempt to better characterize acute and chronic responses to BFR.[5–12] These data have been extensively summarized and reported on in several investigations, systematic reviews, and meta-analyses. Briefly, the skeletal muscle response to BFR and BFR-LIX has been hypothesized to be caused by a combination of contributors including metabolic stress, mechanical loading based stimulation of mechanotransduction sensing mechanisms, autocrine/paracrine hormonal responses to exercise, cell swelling, hypoxia, and generation of reactive oxygen species.[7,13–22] Loenneke et al,[23] hypothesized that the effects of combined BFR-LIX were related to muscle fiber recruitment. Typically, as skeletal muscle fibers fatigue, additional fibers that require a higher stimulatory threshold are recruited to assist in the activity.[24] Because of oxygen restriction and intramuscular metabolite accumulation, it is thought that the resulting fatigue likely drives the recruitment of additional muscle fibers. Skeletal muscle hypertrophy is largely governed by the total volume of mechanical work performed (sets × repetitions × resistance) and the number of muscle fibers utilized to perform that work.[25] In layman's terms, combined BFR-LIX is thought to mimic high volume/HIX in skeletal muscle but is achieved with minimal resistance and reduced risk.

ACUTE ALTERATIONS IN PROTEIN METABOLISM AND ASSOCIATED ANABOLIC SIGNALING (WHAT DO WE KNOW AND WHAT DOES IT MEAN?)

Protein synthesis is a common primary measure by which the efficacy of a particular treatment for stimulating skeletal muscle anabolism in conjunction with mammalian target of rapamycin complex 1 (mTORC1) and mitogen-activated protein kinase (MAPK) signaling pathways[26,27] (Signaling summary shown in Fig. 1). Upon unloading as a result of injury, disease, or

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general disuse, protein synthesis (basal and postabsorptive) has been shown to be suppressed resulting in a loss of muscle mass and function.[28] While highly complex, the mechanisms responsible for this remain unclear but may be associated with immobilization-induced muscle insulin resistance, reduction in amino acid transporter expression, and inflammation-mediated disruption of anabolic signaling, reduced responsiveness of mTORC1 signaling to feeding, and potential inhibition of mTOR-independent anabolic pathways during unloading.[28,29] Aside from suppressed protein synthesis, increased protein degradation, although under much debate, has been hypothesized to contribute to decreased muscle mass following unloading via increased expression of forkhead box O transcription factors (associated with the regulation of protein degradation), activating transcription factor 4, and p53 among other atrophic candidates.[28,30,31]

Regarding BFR therapy, much of the data available have been provided by a limited number of studies.[15–18] Although there are conclusive limitations to our present knowledge of the effects of BFR therapy on skeletal muscle preservation, previous findings from 4 key investigations do provide support for the effectiveness of BFR for stimulating acute muscle anabolism when combined with LIX (BFR-LIX, summarized in Table 1). From these findings, the following conclusions can be drawn about the effects of BFR-LIX on muscle protein metabolism and associated anabolic signaling. Importantly, these data should be considered within the context of the study populations used and the study conditions/protocols implemented (BFR-LIX|performed at 20% or 1 repetition-maximum [1 RM]|Leg extension: 1×30 reps, 3×15 reps|Cuff inflation applied to proximal thigh set at 200 mm Hg|Populations: young and older adult men).

The Effects of BFR-LIX on Muscle Protein Synthesis and Breakdown

- Following an overnight fast, combined BFR and leg extension exercise stimulates an acute increase in muscle protein synthesis immediately following exercise to a similar degree as HIX in healthy young and older adult men (Although, none of the studies in Table 1 used a direct comparison with a HIX group).[15,16] Although not confirmed in the studies presented in Table 1, there is reasonable evidence to infer that this response would be consistent between men and women as the acute protein synthetic response to resistance exercise has been shown to be similar between men and women.[32]

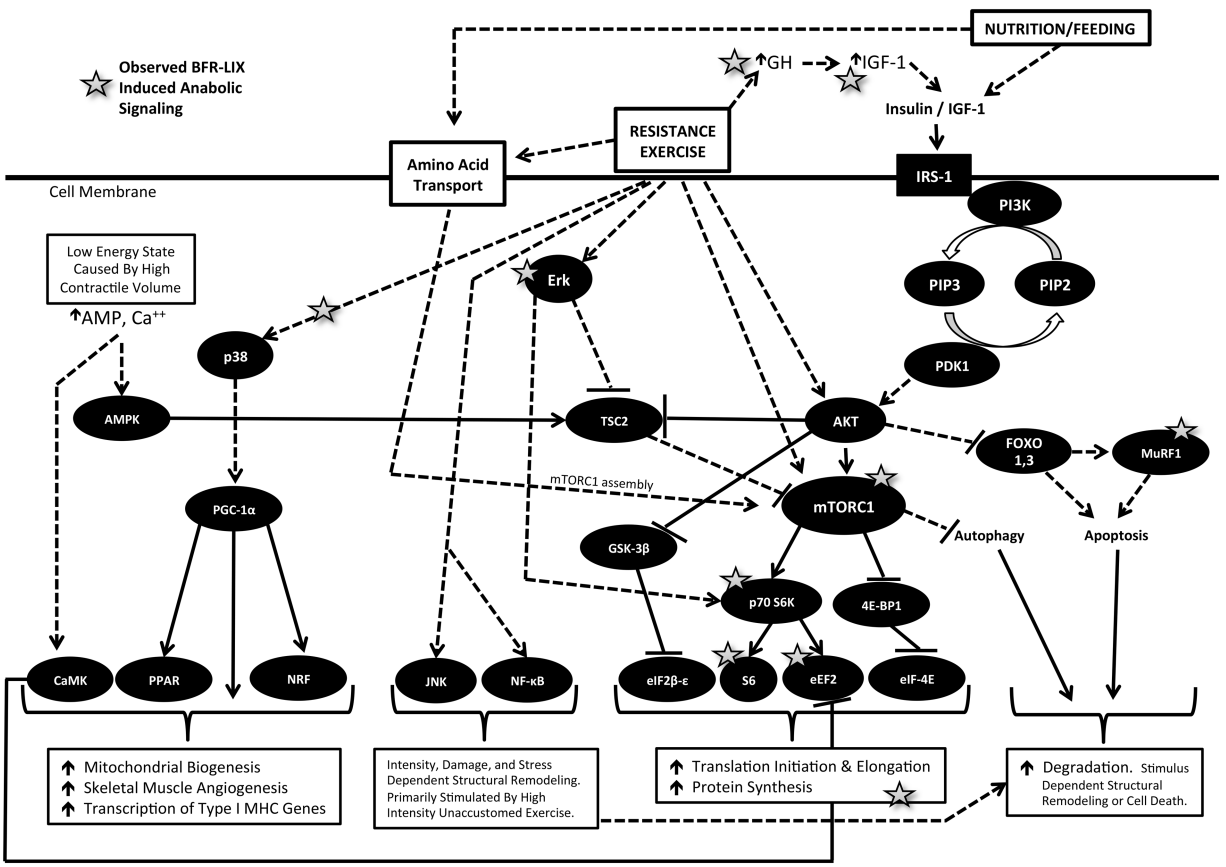

FIGURE 1. Summary of anabolic signaling responses to resistance exercise and amino acids. Solid and dashed lines indicate direct and indirect signaling, respectively. 4E-BP1, eukaryotic initiation factor 4E-binding protein 1; Akt, protein kinase B; AMPK, AMP-activated protein kinase; BFR-LIX, blood flow restriction low-intensity exercise; CaMK, calmodulin-dependent kinase; eIF2β-ε, eukaryotic translation initiation factor 2β-ε; eIF-4E, eukaryotic translation initiation factor 4E, Erk, extracellular signaling-regulated kinase; FoxO 1,3, forkhead box O 1,3; GH, growth hormone; IGF, insulin-like growth factor-1; MuRF1, muscle ring finger 1; GSK-3β, glycogen synthase kinase 3; IRS-1, insulin receptor substrate-1; JNK, c-Jun NH_2-terminal kinase; mTORC1, mammalian target of rapamycin complex 1; NRF, nuclear respiratory factor; NF-κB, nuclear factor kappa light chain enhancer of activated B cells; p38, p38 mitogen-activated protein kinase; PDK1, phosphoinositide-dependent kinase-1; PI3-K, phosphoinositide 3 kinase; PIP_2, phosphotydilinositol^{4,5} bisphosphate; PIP_3, phosphotydilinositol$^{3–5}$ trisphosphate; PGC-1α, PPAR-γ coactivator 1-α; S6K1, p70 ribosomal S6 kinase 1; TSC2, tuberous sclerosis complex 2.

TABLE 1. Summary of Key Mechanistic Investigations on The Acute Skeletal Muscle Response to BFR

References	Study Population/BFR Protocol	Results
Fujita et al[16]	n = 6, recreationally active young men (32 ± 2 y). *BFR method:* KAATSU-Master Mini lower body extremity pressure cuff placed on proximal thigh. *BFR protocol:* Following 4 h basal measurement period, BFR cuff placed and inflated to 120 mm Hg for 30 s followed by release for 10 s and repeated for subsequent increases in pressure of 20 mm Hg until final pressure of 200 mm Hg was reached (maintained at 200 mm Hg during exercise). Exercise protocol: leg extension exercise, 1 set×30 reps@20% 1 RM (30 s rest), followed by 3 sets×15 reps@20% 1 RM (30 s of rest). Exercise time ~5 min. Protocol repeated identically in the same subjects without BFR. *Isotope labeling:* Primed constant infusion of L-[ring-$^{13}C_6$] phenylalanine following overnight fast. Subjects remained fasted throughout the entire measurement period. Total protocol infusion time of ~7 h. Basal protein synthesis (MPS) measures taken and calculated from blood and muscle biopsy sampling at hours 2-4 of the basal measurement period. Postexercise MPS determined from blood and muscle biopsy sampling just prior to exercise and at 3 h postexercise.	*BFR+LIX*: ~45% ↑ in MPS (%/h) compared with basal conditions measured 3 h postexercise. ↑ phosphorylation of S6K1 and ↓phosphorylation of eEF2. ↑ in serum growth hormone and cortisol (60 min following exercise). No changes in serum IGF-1 or testosterone. *LIX only*: ↓ phosphorylation of eEF2 at 3 h postexercise. No change in MPS
Fry et al[15]	n = 7, recreationally active older men (70 ± 2 y). *BFR method and protocol*: Identical to Fujita et al.[16]	*BFR+LIX*: ~60% ↑ in MPS (%/h) 3 h postexercise. ↑ signaling through both mTORC1 and MAPK signaling pathways detected at 1 h and 3 h postexercise. Similar GH and cortisol response observed in young men by Fujita et al. No change in protein breakdown signaling through Akt-FOXO. No change in markers of energetic or hypoxic stress. *LIX only*: ↑ signaling through mTROC1 pathway but not to the same degree as combined BFR+LIX. No change in MPS
Gundermann et al[17]	n = 6, recreationally active young men (24 ± 2 y). *BFR method:* 11 cm-wide pressure cuffs (SC10, Hokanson, Bellevue, WA), placed on the most proximal portion of the upper thighs and attached to a Hokanson E20 rapid cuff inflator and AG101 air source. *BFR protocol:* Identical to Fujita et al. When performed without BFR, the vasodilator sodium nitroprusside (SNP) was administered through a femoral catheter immediately following exercise to closely mimic the postexercise hyperemic response that occurs following BFR+LIX.	*BFR+LIX*: 49% ↑MPS (%/h) compared with basal conditions measured 3 h postexercise paired with ↑mTORC1 and MAPK signaling (similar to Fujita et al and Fry et al). ↑catabolic MuRF1 mRNA expression at 3 h postexercise. ↑Femoral artery blood flow in the early postexercise period (0-10 min) to a greater extent than following LIX+SNP. Greater peak plasma lactate observed compared with LIX +SNP. *LIX+SNP:* Blood flow was closely matched between the LIX +SNP and the BFR+LIX trials but no increases anabolic signaling or FSR were observed
Gundermann et al[18]	n = 16, recreationally active young men (26 ± 1 y). *BFR method*: Identical to Gundermann et al (2012). *Protocol:* Two study groups (n = 8/group; Control and RAP). Both groups performed BFR+LIX. The RAP group consumed rapamycin (known inhibitor of mTOR) 1 h before exercise to inhibit exercise induced mTORC1 signaling. *Isotope labeling and study timeline:* The study involved 2 separate isotope infusions of ~28.5 h. *Day 1, following overnight fast* - Basal measurement period: 2-4.5 h of infusion - BFR+LIX total exercise time (~5 min) - Postexercise measurement period: 0-6 h following BFR+LIX - Tracer infusion stopped at 6 h postexercise. - Subjects fed a meal following completion of day 1 protocol; Subjects fed a second meal in the evening *Day 2* - Following overnight fast a second primed constant infusion was performed from 20-24 h postexercise. - MPS assessed during basal conditions, and between 0-3 h, 3-6 h, and 22-24 h postexercise. [^{15}N]phenylalanine infusion method used to determine fractional protein breakdown rates under basal conditions, 6 h, and 24 h postexercise	*BFR+LIX (control)*: 41.5% ↑MPS (%/h) compared with basal conditions measured 3 h postexercise. Values returned to baseline at 6 h but were again elevated during the 22-24 h postexercise period. *RAP treatment group*: MPS was unchanged from basal rates at all measurement time points although there was a trend toward an increase during the 22-24 h postexercise period. ↑mTORC1 signaling observed in the Control but not the RAP group. No change in protein breakdown rates observed

Akt indicates protein kinase B; eEF2, eukaryotic elongation factor 2; FoxO, forkhead box O; GH, growth hormone; IGF-1, insulin like growth factor; MAPK, mitogen activated protein kinase; MuRF1, Muscle RING finger 1; MPS, muscle protein synthesis; mTORC1, mammalian target of rapamycin complex 1; S6K1, p70 ribosomal S6 kinase 1; RAP, rapamycin.

- The initial protein synthetic response seems to be transient as Gundermann et al[18] observed a return to basal levels at 6 hours postexercise. While later increases in muscle protein synthesis were observed during the 22 to 24 hours postexercise period (indicating a biphasic response), subjects were fasted throughout the initial phase of the study and it is unclear as to how 2 instances of feeding taken after 6 hours postexercise might have contributed to subsequent elevations at later time points. Previous data indicate an additive effect of nutrition when provided following exercise.[33–35] Therefore, although there may be multiple additional stimuli responsible for the biphasic response observed, it is likely that the provision of meals following the initial infusion protocol may have contributed to the increases in protein synthesis via supplying of nutrients following prolonged fasting.
- Alterations in muscle protein breakdown do not seem to play a role in the acute skeletal muscle response to short duration BFR-LIX.[18] However, this conclusion should be guarded with caution. The hypothesis that the lack of impact of BFR-LIX on muscle protein breakdown provides an additional benefit to the process of exercise adaptation beyond HIX may be misleading and may not take into account that structural remodeling typically associated with resistance exercise and provides an important function of maximizing functional muscle quality during adaptation.[36–39] Of note, muscle ring finger protein 1 (MuRF1) mRNA expression was found to be elevated immediately following exercise to a similar degree as previously observed with HIX, which may be indicative of some degree of proteolytic driven remodeling.[17] Whether or not a reduced impact on muscle protein breakdown yields any adaptive benefits remains unclear. Furthermore, without direct measure of signaling, synthesis, or degradation, the assumption that activation of mTORC1 or other growth associated pathways is a simultaneous indicator of inhibition of degradation/autophagy pathways may also be misleading as cell signaling cross-talk is complex and responsive to a variety of physiological factors such as cell energy status, nutrient availability, and stress.[26,40,41] Importantly, it may be advantageous to evaluate the effects of BFR with regards to preventing atrophy or altering protein degradation in a long-term unloading model (days/weeks) with higher resemblance of the unloading conditions experienced by patients to determine to what degree BFR therapy may play a role in reversing atrophic signaling and related skeletal muscle loss.

The Effects of BFR-LIX Skeletal Muscle Anabolic Signaling

- The anabolic responses to BFR-LIX are largely dependent on an increase in mTORC1 signaling via mechanisms that have yet to be fully revealed.[18] This conclusion is largely based on the finding that inhibition of mTORC1 with rapamycin blunts muscle protein synthesis following BFR-LIX.[18]
- A concurrent acute increase in MAPK signaling is present following combined BFR-LIX and may provide an alternate pathway independent of mTORC1 signaling that may be required for maximal activation of protein synthesis following BFR-LIX.[15,17,18] In the case of BFR, MAPK signaling (Akt ERK, p38 MAPK) may be increased as a result of mechanisms involved in mechanotransduction or cell stress associated with muscle cell swelling.[42] However, the underlying mechanisms by which this may occur remain unclear.

Acute Hormonal Responses to BFR-LIX

- BFR-LIX elicits an acute transient increases in systemic growth hormone (GH),[15,16] a positive regulator of cellular differentiation[11,33] that may or may not play a role in direct stimulation of muscle protein synthesis. Although indirect anabolic signaling through GH-stimulated release of insulin-like growth factor-1 (IGF-1) has been postulated to play a role in exercise-mediated acute responses to BFR-LIX,[12,22] much is still unknown regarding the autocrine or paracrine role of IFG-1 with regards to stimulation of postexercise increases in protein synthesis via mTORC1 signaling. In the case of the results presented in Table 1, the exercise treatments did not elicit any systemic alterations in systemic IGF-1. However, it cannot be discounted that local skeletal muscle–derived IGFs rather than systemic IGF-1 may act in an autocrine manner to regulate growth under conditions of stress and hypoxia that occur during BFR.[43] Local IGFs have been previously observed to act on both mTORC1 and MAPK signaling pathways to regulate skeletal muscle differentiation and proliferation.[43] Both GH and IGFs have also been shown to play a role in satellite cell proliferation and differentiation during recovery from exercise[43,44] and may account for more long-term adaptations to BFR-LIX. Of note, both Abe et al,[45] and Takano et al,[46] did observe chronic (2 wk) and acute (10 to 30 min) increases, respectively, in systemic IGF-1 following BFR-LIX. However, the degree to which either IGFs or GH signaling mechanisms are responsible for acute increases in protein synthetic responses to BFR-LIX in comparison to HIX remain unknown.
- Alterations in testosterone do not seem to play a role in the acute response to BFR-LIX as enhanced anabolism was observed in a similar manner to HIX (although not directly compared) in the absence of elevations in serum testosterone.[16] These findings are further supported by previous observations that acute postexercise anabolism is not primarily governed by transient changes in systemic testosterone concentrations.[47–50]

Reactive Hyperemia Following BFR-LIX

- Enhanced nutrient delivery via reactive hyperemia observed following BFR-LIX does not seem to contribute to elevations in postexercise muscle protein synthesis. This was demonstrated by Gundermann et al,[17] as sodium nitroprusside (vasodilator) infusion following LIX was unable to replicate the postexercise anabolic response of BFR-LIX indicated that other mechanisms may play a role.

Stress Response to Exercise

- BFR-LIX yields increases in blood lactate and alterations in blood pH that are similar to HIX,[15–18] a finding consistent among several investigations.[51,52] Recent evidence suggests that increasing local and systemic concentrations of lactate and calcium through either stress or pharmaceutical means may chronically increase satellite cell differentiation and

skeletal muscle growth via calcineurin dependent signaling.[53] In the case of BFR-LIX, muscles are exercised to fatigue in an environment that prevents (temporarily), the flushing out of metabolites, and thus providing a metabolic environment more prone to stress signaling. It is possible that the exercise stress responses observed with BFR-LIX in concurrence with increased fiber recruitment due to metabolic fatigue, increased, structural strain from muscle cell swelling, and potential release of local myokines may provide the greatest overall stimulus during BFR to elicit anabolism.[44]

Methodological Considerations

The investigations listed in Table 1 utilized a traditional primed constant stable isotope infusion model.[15–18] While measures of protein synthesis using stable isotope infusion (using $^{13}C_6$-Phe, a labeled amino acid tracer) are commonplace for evaluating the effects of exercise on muscle, previous measurement timelines and techniques for assessment of BFR may be limited with regards to their conclusive value.[54] To briefly summarize, in order to quantify protein synthesis a label must be used so that amino acids can be traced as they are incorporated into new protein (in the case of this study, muscle). If one provides (orally or intravenously) a certain dosage of label, it can be examined in both the blood stream and in muscle as it is transported into the cell and incorporated into muscle protein (growth) using mass spectrometry.[55] This is calculated by using the ratio of tracer (labeled amino acids) to tracee (unlabeled amino acids) and then determining how the ratio of tracer:tracee changes over time.[55] Therefore, the greater the change in muscle bound protein across a given time span, the greater the rate of protein synthesis.[55] One consideration with the method utilized in the studies shown in Table 1 is that it involves infusion of prelabeled amino acids (often $^{13}C_6$-Phe) and is highly dependent on the amino acid precursor pool remaining stable over time.[54] Because dietary protein is a nutritional amino acid source, any feeding that occurs during the measurement period results in a disrupted precursor pool in which case, measures become invalid.[54] At best, using this method, temporary snap shots of protein synthesis can be taken over long periods of time in a fasted state in a manner that is not necessarily analogous to the free-living conditions where nutrition, overall energy status, nutrient absorption, and nutrient sensitivity have been shown to be highly interrelated dynamic contributors to the cumulative acute increases in muscle anabolism that may last between 48 and 96 hours postexercise.[54] Additionally, across large timelines, gaps in labeling / measurement periods do not account for variation inter-individual variation and also do not account for differences related to training status or age.[49] For example, previous investigations suggest that individuals with different training statuses (experienced compared with inexperienced) experience peak muscle protein synthesis at different points following exercise.[49] Therefore, comparative conclusions based on specific time points likely do not account for the cumulative effect of exercise on muscle protein synthesis and may not be predictive of long-term gains in lean body mass. Deuterium oxide ingestion (^2H_2O) has become a popular method for studying the effects of exercise and nutrition on muscle protein synthesis across days and/or weeks.[54,56–58] An advantage of this method is that labeling of amino acids occurs internally via metabolic reactions involving water. The method is less invasive compared to primed-constant infusion protocols and measurements periods can occur in the fed state[54] This allows for a more accurate account of the anabolic response to exercise in free-living conditions over large timelines (24 h to weeks).[54] Therefore, future BFR studies may benefit from this labeling approach. Through the use of ^2H_2O labeling, future investigators may be able to identify peak time points within differing populations of various age ranges, unloading conditions, and injuries at which the protein synthetic effects of BFR are observed.[47] Of related clinical value, because ^2H_2O labeling can be performed in the fed state, the cumulative effect of combined nutritional and exercise interventions may be observed across days or weeks.[47] These benefits will likely aid in optimizing treatment protocols with regards to volume, intensity, duration, and frequency may be further refined for given target populations and injury types.

While comparisons can be drawn from previous literature on HIX using the same methods for quantifying postexercise protein synthesis, no direct comparisons were made in the investigations presented in Table 1.[15–18] Current hypotheses may benefit from refinement and differentiate between varying exercise intensity and volume thresholds. For example, 70% of 1 repetition-maximum (1 RM) performed for 8 sets of 10 repetitions to failure has been frequently utilized as a HIX model under similar isotope infusion protocols to those described in Table 1.[59–61] However, Burd et al,[62] has previously demonstrated that the protein synthetic response to exercise is greater following LIX performed at high volumes compared with HIX performed at lower volumes. Therefore, further research may be required to more adequately determine the acute and chronic responses to BFR-LIX compared with LIX (> 40% 1 RM), moderate intensity (40% to 70% 1 RM), or HIX (70% to 100% 1 RM). Future investigations should consider separate comparisons for alterations in strength, endurance, range of motion, and changes in muscle mass and determine which factors are of most importance for given therapeutic interventions. For example, the goals of young injured athletes likely involve return to sport, regain of muscular strength, and optimal performance, whereas the goals of elderly individuals may primarily involve maintenance of skeletal muscle mass and functional stability.

Although methodological limitations are present in previous investigations, the findings presented in Table 1 have provided an invaluable foundation of support for the efficacy of using BFR therapy to combat skeletal muscle loss. These studies have also provided a pathway of focus for future investigators. Crucially, while acute postexercise protein synthesis measures were a primary focus, associated anabolic signaling as well as hormonal, stress, and hemodynamic responses were observed in conjunction. These studies also highlight specific intracellular signaling pathways involved and how they may be triggered; thus providing conclusive advantages over making inferences that acute alterations in hormone or stress marker concentrations alone are indicative of, or the mechanisms responsible for, growth and hypertrophy without direct measures of anabolism. The findings of these works have also set forth the groundwork for the development and practice of evidence-supported clinical rehabilitation protocols and guidelines. Although much is left to be determined with regards to optimization of rehabilitation protocols and proper patient targeting, the clinical use of BFR as a therapeutic tool, has proved to be invaluable in allowing clinicians, therapists, and researchers to determine (1) the clinical efficacy and practicality of BFR; (2) safety considerations from field observation; (3) exercise selection and adaptation of BFR protocols; (4) the identification of further pressing questions and concerns to be addressed by additional basic and applied investigations.

Overview: BFR in Physical Therapy Settings

PT are active in the recovery and rehabilitation of various ailments and injuries. A PT will commonly treat individuals who are limited in their function of daily or recreational activities. Through intricate evaluative processes and ongoing clinical assessment, a therapist will target specific impairments and provide treatment through a variety of methods: therapeutic exercise, neuromuscular reeducation, manual therapy, and therapeutic modalities. Ultimately, a patient's goals, available evidence, and clinician experience will guide treatment protocol in an effort to maximize the patient's potential for rehabilitation.[63]

Dysfunction of the musculoskeletal system, in particular, often provides challenges for the patient and rehabilitation professional, alike. Often, pain and dysfunction present in damaged muscle or connective tissues. Range of motion, muscular strength, and neuromuscular control may commonly be affected, leading to continued impairment and deficiencies in functional ability. Muscular weakness is a large contributor to functional impairment and strengthening programs are frequently implemented by PTs to stimulate muscular hypertrophy and subsequent strength gains. However, strengthening may be challenging for an individual in pain.

The American College of Sports Medicine recommends that novice and intermediate lifters use 75% to 85% of their 1 RM for strength training to induce hypertrophy over 12 to 16 weeks.[64] Unfortunately, a structured HIX program may not always be feasible for the average individual rehabilitating an injury. Following muscle and/or ligament tears, tendon complications, or surgical procedures, patients are typically limited in their ability to perform activities with high loads in an attempt to protect the tissues' integrity. Thus, the challenge for most therapists is to mitigate muscle atrophy while promoting an optimal environment for healing.

In an effort to limit the atrophic response following injury or surgery, rehabilitation professionals have begun implementing BFR in their strengthening protocols to improve function and reduce pain.[65–68] A recent systematic review concluded that the growing body of evidence indicates that BFR can produce "positive training adaptations at intensities lower than previously believed."[12] Another review indicated that "BFR alone can attenuate muscle atrophy during periods of disuse."[6] Therefore, individuals who are impaired by weakness and pain or those who are restricted from HIX due to postsurgical precautions can experience a productive training response with BFR-LIX protocols. Furthermore, individualized BFR training may provide a comparable surrogate for heavy-load training while minimizing pain during training.

BFR AND PHYSICAL THERAPY FOLLOWING KNEE LIGAMENT RECONSTRUCTION

Individuals who undergo ligamentous reconstruction of the lower extremity are often plagued with weakness and dysfunction. In the case of anterior cruciate ligament (ACL) reconstruction, quadriceps weakness predominates as one of the greatest impairments following surgery.[19,69] Insufficiency of the extensor complex of the knee can lead to decreased function[70,71] and increase the probability of an unsuccessful return to sport,[72] reinjury,[73–76] or the development of knee osteoarthritis later in life.[77–79]

In an effort to prevent significant quadriceps atrophy following ACL reconstruction, PT have utilized various tools including "prehabilitation," electrical stimulation, biofeedback, and early isometric activities to accelerate function and strength.[80,81] Several studies have demonstrated the positive effects of BFR in early phases of rehabilitation following ACL reconstruction[11,82,83] with regards to preservation of muscle mass and function. However, Iversen et al[83] demonstrated that a small group of patients did not experience the same effects of atrophy mitigation in the early rehabilitative phases utilizing BFR.

Early after surgery, ACL patients may perform low-level isometrics, such as quad-sets, with BFR to improve muscle activation.[13] For those who are also limited in weight-bearing status (eg, following concomitant microfracture surgery), positive benefits can be expected from BFR combined with lower-level isometrics and open-chain activities to prevent further atrophy before returning to full weight-bearing. As the individual progresses in tolerance and weight-bearing status, they may progress to more functional activities with BFR, using lower loads at high repetitions. As previously used in other studies, the 30-15-15-15 repetition protocol seems to be effective for improved rehabilitation outcomes.[6] However, clinical outcomes with regards to return-to-sport measures among athletes who undergo ACL reconstruction and utilize BFR during the course of therapy are not well known.

BFR THERAPY AND TOTAL/PARTIAL JOINT REPLACEMENT

Patients who undergo total joint arthroplasty of the lower extremities, including total knee arthroplasty (TKA) and total hip arthroplasty, experience similar impairments to postoperative ACL patients. Frequently, individuals may lose up to 80% of their knee-extension strength in the first few days following TKA —especially those with extended hospitalizations.[84] Following total hip arthroplasty, patients experience a substantial loss in overall hip and quadriceps strength.[85–88] The deleterious effects of muscle loss in these patients hinder functional improvement and lengthen recovery times.

Typically, most individuals are allowed to bear weight early after joint replacement surgery, but are still restricted from HIX or impact-related activities for indefinite periods of time. Therapists are able to utilize low-level strengthening exercises (eg, light leg press, straight leg raises, long-arc quads, body-weight squats) to elicit a productive strengthening response. This lessens the load experienced by the prosthetic and surrounding tissues, decreasing pain and inhibition experienced with early postsurgical phases of rehabilitation. Furthermore, patients can potentially experience quicker return to function due to diminished muscle loss and improved strength, advancing their rehabilitation even further.

In the case of prearthroplasty, most patients experience significant osteoarthritis in the affected joints. Pain and dysfunction are common due to the degenerative effects to the joint surfaces. In some cases, significant weakness can be expected in associated musculature around and associated with these joints.[89,90] These individuals may not be able to pursue high-intensity training and can be unsuccessful in attempts to avoid surgery due to persistent weakness. Therefore, the utilization of combined BFR-LIX may provide patients with pain symptom relief as well as higher success rates in conservative care. The inclusion of BFR in preoperative exercise has shown initial promise in improving strength before TKA.[91] Furthermore, early results are positive in BFR training programs for those at risk for symptomatic knee osteoarthritis.[92]

BFR FOR PROXIMAL RATHER THAN DISTAL BENEFIT

To exercise with BFR, one must apply a pressure-controlled tourniquet to the most proximal portion of the limb

being trained. For the lower extremity, the cuff would be placed at the proximal thigh, just distal to the inguinal crease. In the upper extremity, a cuff would be placed just distal to the axilla. In order to prevent complications due to pressure over a peripheral nerve (neurapraxia), the tourniquet is used over regions with higher mass and limb width. Unfortunately, there are no tourniquet cuffs that would isolate muscle groups more proximal to the limbs. Therefore, one may speculate that muscles proximal to the occlusion cuff may not experience similar strength gains as found in those distal to the cuff. However, a systematic review by Dankel et al,[93] found several instances of proximal gains in muscle size and strength. They noted that the BFR stimulus is effective in increasing muscular strength of the shoulder and back musculature, but may require a greater volume of exercise compared with those muscles distal to the applied cuff.[93]

Suggested mechanisms for this phenomenon include the typical high repetition characteristic of BFR exercises (upwards of 75 total repetitions per exercise), purported synergistic effects of proximal musculature as the distal muscles fatigue and higher recruitment of type II muscle fibers, and muscle cell swelling occurring during BFR.[20,21,94] For an individual who is seeking physical therapy following a rotator cuff tendon repair, they will be restricted in early active movement and strength progressions for upwards of 10 to 12 weeks.[95] During this time, significant loss in strength of the surrounding musculature can be expected. With the addition of BFR in early phases of rehabilitation, patients may experience better short-term and long-term outcomes. However, the effects of BFR following rotator cuff surgery have not yet been studied.

BFR THERAPY AND UPPER BODY REHABILITATION

When performing BFR on upper body musculature, one must take into account the smaller limb circumference and girth in this region.[93] In current studies examining BFR for the upper extremity, occlusion pressures seem to be grossly arbitrary and inconsistent.[93] On the basis of the data available, exercises may be performed with the same repetition scheme as with the lower extremity, but some studies indicate that proximal upper extremity muscle groups will require greater repetitions (up to 165) to achieve comparable improvement.[93] Several benefits have been observed for musculature in the chest, back, shoulders, and arms,[93] with regards to rehabilitative upper extremity strengthening at lower loads. Individuals who suffer from complications due to tendinosis, ligament rupture, or fracture may be able to improve their upper extremity function utilizing BFR during rehabilitation. Outcomes for BFR with specific upper extremity injuries are largely unknown at this point and provide an intriguing paradigm for future research.

CONCLUSIONS AND CONSIDERATIONS FOR FUTURE RESEARCH

In conclusion, combined BFR-LIX stimulates an increase in both acute and chronic skeletal muscle anabolism at loads under 30% 1 RM and provides therapists with a tool for combating skeletal muscle loss and accelerating rehabilitation following injury and/or surgery. While the exact mechanisms that govern skeletal muscle responses to BFR have yet to be completely elucidated, current data indicates that BFR yields a postexercise stress response that mimics HIX. Importantly, many current rehabilitation protocols involving BFR have been developed under a degree of assumption and extrapolation from initial BFR investigations. Accordingly, future studies are needed to further determine the underlying mechanisms that govern muscle responses to BFR and BFR-LIX under varying exercise types, volumes, and intensities.

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The Role of Blood Flow Restriction Training to Mitigate Sarcopenia, Dynapenia, and Enhance Clinical Recovery

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Summary: Aging is associated with progressive losses of muscle mass (sarcopenia) and strength (dynapenia) leading to reduced functional capacity. Traditional aerobic and resistance exercises are commonly recommended to enhance health and mitigate aging-related performance concerns. Recently, blood flow restriction (BFR) exercise has gained scientific merit as a hybrid aerobic and resistance exercise intervention that may be suitable for application in older adults and following musculoskeletal injury to both mitigate and treat the resulting sarcopenia or dynapenia. Muscle hypertrophy ranging from <1% to 2.6% per week and muscle strength gain ranging from <1% to 5.9% per week have been reported following BFR exercise training when combined with various methods (walking, body weight, elastic bands, and traditional weight training). Further, given the projected increase in orthopedic surgeries in the aging population, the anabolic potential of BFR exercise methodology has gained additional interest the area of clinical rehabilitation following musculoskeletal insult. In particular, older adults recovering from various medical procedures may benefit from BFR exercise in order to regain muscular strength and size during recovery to avoid any additional complications from anabolic resistance, weakness, or disuse. Although care should be taken when selecting BFR exercises over traditional therapy interventions, there is evidence BFR exercise is a suitable intervention to mitigate sarcopenia and dynapenia and enhance muscle strength and mass recovery following various clinical conditions. Further, as BFR exercise provides an additional intervention to improve functional capacity by increasing muscle strength, mass and endurance, it's utility in mitigating sarcopenia and dynapenia in at risk individuals (ie, frail elderly, postoperative) is becoming more apparent.

Key Words: sarcopenia—dynapenia—exercise—rehabilitation.

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In the United States the number of adults over 65 years of age is projected to increase from 40 million in 2010 to 86.6 million by 2050.[1] With advancing age there are numerous physiologic changes occurring within the body's systems, among the most noticeable is loss of muscle mass. Rosenberg[2] introduced the term sarcopenia (loss of flesh) to describe this phenomenon. As of September 2016, Sarcopenia is now recognized as a unique disease with a ICD-10-CM code.[3] Although agreement of what constitutes the best assessments to define sarcopenia is not universal, the European Working Group on Sarcopenia in Older People has established some guidance for clinical practice and diagnosis.[4] Sarcopenia can be defined by the loss of lean muscle mass (skeletal muscle index, men $\leq 8.90\ kg/m^2$, women $\leq 6.37\ kg/m^2$) and loss of physical performance (gait speed, ≤ 0.8 m/s) and/or strength (handgrip, men <30 kg, women <20 kg).[4–6] The latter 2 factors of this definition also refer to attributes of strength and power. Further, some researchers have argued that losses in strength are independent of losses in mass and have termed these age related losses of strength as dynapenia.[7] Emerging evidence supports the loss of strength as a negative factor in well-being as one ages,[8] with the overall the loss of total muscle strength affecting about 5% of persons aged 65 years and up to 50% of the population over 80 years.[9–11]

Many interacting factors contribute to the natural progression of sarcopenia and dynapenia[12] including a decrease in the number of motor neurons, nutritional deficiencies, a lack of physical activity, and a decline in anabolic hormone production.[13] Increasing general physical activity and participating in structured aerobic and resistance exercise training have been advocated for older adults as a method to improve health and mitigate aging-related conditions.[14] Structured resistance training, in particular, appears efficacious; unfortunately many older adults do not participate resistance training because of barriers such as fear of falling or their current physical ailments.[15]

In addition to the natural progression of sarcopenia and dynapenia, muscular disuse following hospitalization, musculoskeletal procedures, accidents, or prolonged hospital or cast immobilization can rapidly decrease muscle mass and strength loss.[16,17] Consequently, a preoperative patient may not meet the criterion for sarcopenia or dynapenia upon initial consultation, but the metabolic stress and acute musculoskeletal insult that occur following many orthopedic procedures may cause patients to lose muscle mass and strength, leading to a secondary progression of sarcopenia and dynapenia. This secondary progression is consistent with studies showing a clinically significant decrease in function following lower extremity total knee arthroplasty, arthroscopy, and musculoskeletal injury. Furthermore, as the number of total knee arthroplasties continue to increase, with a projected 673% increase in the United States by 2030 alone, the clinical functional recovery and economic burden of the postoperative recovery become increasingly relevant.[18] Likewise, as a significantly higher proportion of orthopedic procedures will be in patients 65 and older,[19] novel and effective exercise rehabilitation strategies are needed.

Recently a new approach to preventative and rehabilitation exercise termed blood flow restriction (BFR) has gained scientific merit. BFR exercise relies on performing physical activity at low physiologic loads in a state of partial vascular

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occlusion to induce metabolic changes that allow a physiologic increase in muscle strength, endurance, and mass. This can allow a more rapid progression of strength and function in those patients unable to participate in high-load resistance training. The purpose of this review is to provide a scientific rationale for the use of BFR related exercises to mitigate sarcopenia and dynapenia. Further, this manuscript will evaluate BFR exercise as a rehabilitation intervention from muscle loss and weakness as a result of aging and during recovery following medical procedures.

BFR EXERCISE TO MITIGATE SARCOPENIA AND DYNAPENIA

The mechanisms for how BFR exercise creates a potent anabolic environment for adaptation have been reviewed in detail.[20–22] In brief, the combination of localized muscular hypoxia enhances glycolytic cellular metabolism, triggers anabolic hormone responses (eg, growth hormone), and activates cell-signaling cascades to increase protein synthesis and suppress protein degradation.[23–27] These changes create the requisite anabolic environment for muscle cell hypertrophy.[28] For the mitigation of sarcopenia and dynapenia, there may be several potential advantages of exercising with blood flow restriction versus traditional techniques. Resistance exercise generally requires training loads of 70% to 85% one repetition maximum (1RM) to optimize gains in muscle strength and hypertrophy.[14,29] Exercising with BFR is typically performed at 15% to 30% of 1RM[21] resulting in muscle strength and hypertrophy increases that are comparable to traditional high-load methods.[30] Exercising at lower physiological loads also allows for a substantial reduction in mechanical loading of muscle, bone, ligaments, and tendons that may be advantageous in those patients unable to achieve higher levels of physiologic loading because of medical comorbidities or postoperative restrictions. This may accommodate those who have little experience with resistance, or weight lifting, methodology and provide a safe opportunity to build proper exercise technique and ensure a full range of motion with less musculoskeletal demand and a lower joint reaction force.

The reduction in mechanical loading does not blunt hypertrophy related cell-signaling within the muscle tissue. In younger adults, BFR exercise seems to help foster an anabolic environment by increasing muscle protein synthesis 3 hours post exercise by activating the mammalian target of rapamycin pathway (mTORC1) leading to increased muscle protein translation.[24] This mechanism does not seem to change in older adults. Fry et al[23] showed that muscle protein synthesis increases 56% 3 hours following low intensity exercise with blood flow restriction, whereas there was no change in the same exercise without the inflated restriction cuff in older adult men. Further, a downstream effector of mTORC1 activation, ribosomal s6 kinase 1, was significantly enhanced following BFR exercise.[23] This suggests that BFR exercise may overcome anabolic resistance, which is the inadequate stimulation of muscle protein synthesis following an anabolic stimuli such as exercise or feeding.[31] In older adults, BFR exercise has been combined with walking,[32–35] body weight exercise,[36] elastic bands,[37,38] and traditional resistance exercise.[30,39–43] This flexibility creates several different opportunities for older adults to engage in BFR exercise and may provide a framework for progression and treatment, where older adults can begin with walking exercise and progress toward more difficult modalities of resistance exercise. Research studies exploring different types of BFR exercise in older adults are discussed below.

BFR Walking Exercise

Investigations exploring BFR walking exercise have lasted between 6 and 10 weeks in duration.[32,34,35,44] Typically, in these studies BFR exercise has been performed at a frequency of 4 to 5 days per week for a duration of 20 minutes at an intensity of ~45% of heart rate reserve. Although low intensity walking alone does not increase muscle size or strength, there seems to be evidence that low intensity BFR walking may provide a potent enough stimulus to trigger muscular adaptation.[32,34,35,44] Figure 1 shows the change (%) in muscle strength (A) and hypertrophy (B) following BFR walking and control walking without BFR in older adults. These anabolic muscular adaptations have also been accompanied by 10% to 12% and 14% and 30% improvements in timed up and go tests and chair stand tests, respectively.[32,35,44]

BFR Body Weight Exercise

To our knowledge, only one study has paired BFR exercise with body weight exercise among older adults (~70 y).[36] Yokokawa et al[36] paired 6 different exercises with BFR over an 8-week training program. Exercises included half squats, forward lunges, calf raises, knee lifts, crunches, and seated knee flexion and extension. The BFR body weight exercise program was compared to a 90-minute dynamic balance exercise program designed to enhance posture and dynamic stability through exercises such as: forward and lateral reach, forward

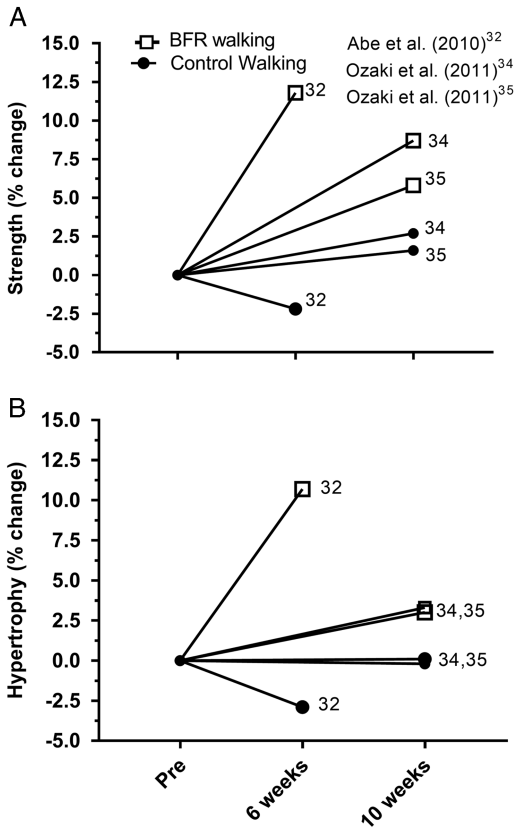

FIGURE 1. Strength (A) and hypertrophy adaptations (B) with BFR walking and control walking in older adults (57 to 78 y). Abe et al[32] = 6 weeks. Maximal isometric strength and ultrasound muscle thickness measurements were performed. Ozaki and colleagues = 10 weeks. Maximal isometric strength and magnetic resonance imaging measurements were performed. Studies examined are referenced here.[32,34,35]

and backward steps, standing and walking on a reduced base of support. Reaction time, maximal step distance, 10 m walk time, functional reach, and standing on 1 leg tests all improved in both groups. BFR body weight training showed significant improvements over the dynamic balance training for timed up and go (20%) and knee extension strength (23%).

BFR Elastic Band Training

BFR Elastic band resistance exercise has been generally performed 2 to 3 days per week for 8 to 12 weeks in older adults (59 to 85 y).[37,38] Thiebuad et al incorporated elastic band exercise for seated chest press, seated row, and shoulder press,[38] while Yasuda et al[37] utilized arm curl and triceps press down exercises. Participants in both studies showed significant improvements in muscle strength (5% to 16% in various muscle groups tested),[37,38] whereas Yasuda et al[37] also showed hypertrophy of the elbow extensor (17%) and flexor muscle groups (17%).

BFR Traditional Resistance Exercise

BFR combined with traditional resistance exercises have been performed 2 to 3 days per week for 4 to 12 weeks in older adults (50 to 73 y).[30,39–43] Figure 2 shows the amount of strength gained relative to the duration of the BFR resistance exercise training (A) or traditional resistance exercise training (B) in various muscle groups tested. Similarly, Figure 3 shows the change in muscle hypertrophy relative to the duration of BFR resistance exercise training (A) or traditional resistance exercise training (B) using various assessment methods (MRI, CT, Ultrasound). BFR resistance exercise has been performed at a low intensity (20% to 30% 1RM) and seems to result in strength and hypertrophy adaptations that are not statistically different to heavy resistance exercise (70% to 80% 1RM).[30]

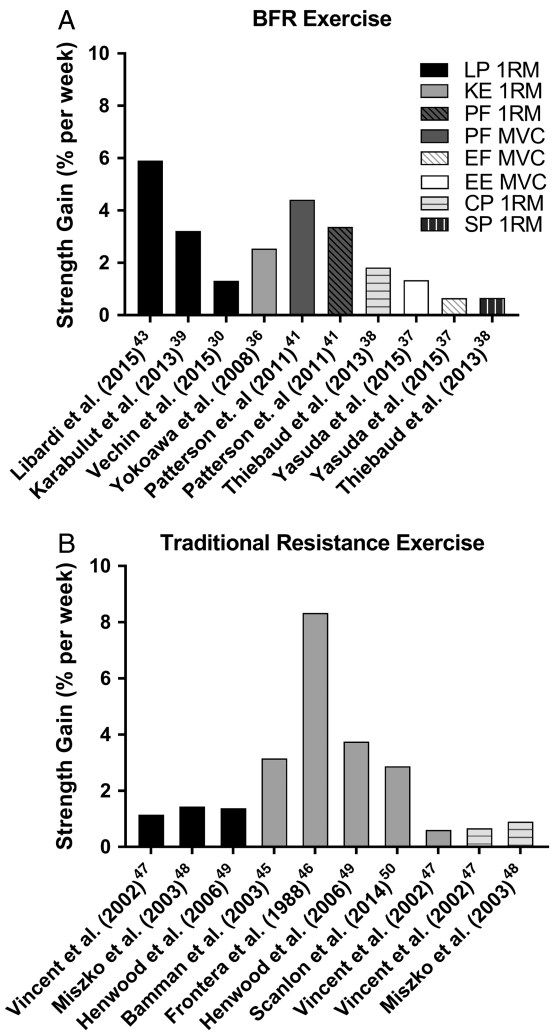

FIGURE 2. Relative strength gain per week for BFR resistance exercise (A) and traditional resistance exercise (B) in older adults. 1RM indicates one repetition maximum; CP, chest press; EF, elbow flexors; EE, elbow extensors; KE, knee extension; LP, leg press; MVC, maximal voluntary isometric contraction; PF, plantar flexion; SP, shoulder press. Studies examined are referenced here.[30,36–38,40,41,43,45–50]

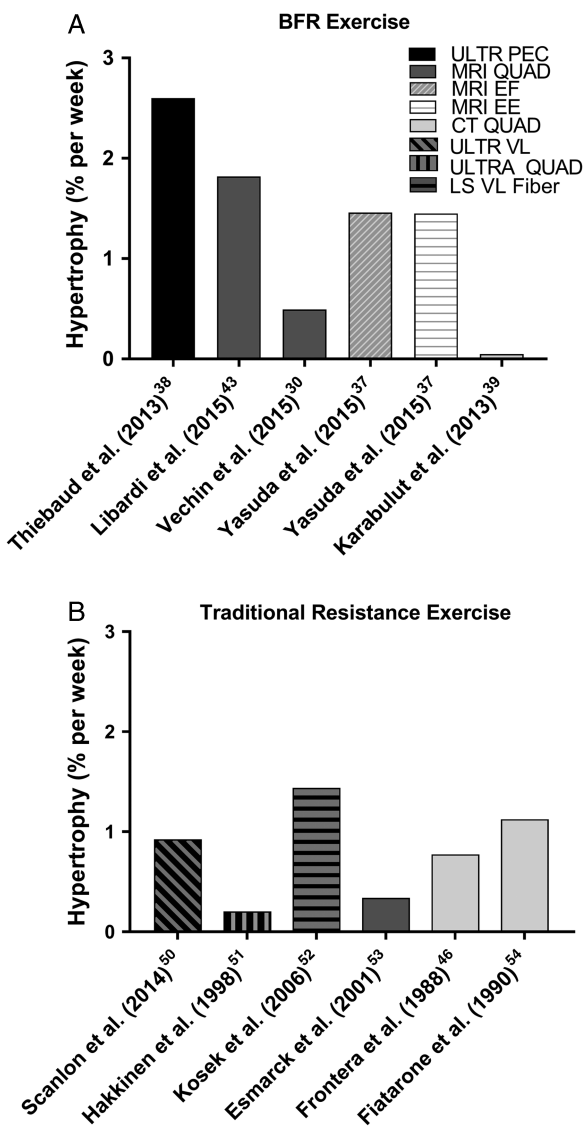

FIGURE 3. Relative hypertrophy per week for BFR resistance exercise (A) and traditional resistance exercise (B) in older adults. CT indicates computerized tomography; EE, elbow extensors; EF, elbow flexors; LS, lamin staining; MRI, magnetic resonance imaging; PEC, pectoralis major; QUAD, quadriceps muscle group; ULTR, Ultrasound; VL, vastus lateralis. Studies examined are referenced here.[30,37,38,40,43,46,50–54]

CLINICAL APPLICATION OF BFR EXERCISE TRAINING

Although the detrimental effects on physical function and mobility because of an overall decrease in muscle mass are quite obvious, the secondary effects of decreased muscle mass also must be considered.[10,55] Skeletal muscle is a principal reservoir for amino acids which are critical for recovery following acute infection or trauma and it influences energy requirements through the modulation of resting energy expenditure.[55] Several studies have also correlated a decrease in muscle mass with increased systemic hormonal dysregulation and increased cardiovascular and metabolic disease.[56–58] Increases in these comorbidities in combination with a generalized loss of quadriceps strength can increase safety concerns in the elderly population as quadriceps strength has been associated with inhibited balance, decreased ambulatory capacity and an increased incidence of falls. As such, interventions focused on mitigating the falls risk may help mitigate the resulting morbidity and mortality associated with commonly encountered hip fractures in this population.[59–62]

In addition to restoration of range of motion, recovery of postoperative strength is paramount to functional recovery following lower extremity surgery. In particular, quadriceps inhibition has been shown to correlate with patient functional and reported outcomes following routine knee arthroscopy, anterior cruciate ligament (ACL) reconstruction and total knee arthroplasty, which can diminish to 30% to 60% of preoperative levels within 4 weeks of surgery.[63–70] Although the current American College of Sports Medicine (ACSM) rehabilitation guidelines specify that a minimum of 70% to 80% of a patient's 1RM is required to induce significant strength gains, these weights are not always possible because of postoperative restrictions or a variety of patient related factors.[14,71,72] In these patients, a prolonged course of physical therapy and a delay to full recovery can be seen which can increase the overall cost of health care.

Functional recovery following lower extremity trauma has also been well documented and is frequently associated with an overwhelming loss of muscular strength and endurance secondary to the increased metabolic stress of the inciting injury and subsequent recovery from surgery. These patients frequently require prolonged multimodal therapies and often reach a state of chronic muscle weakness and an inability reach preinjury functional return to activity several years following their injuries.[73–76] Furthermore, in a recent study by Kaplan et al,[77] sarcopenia was found to be an independent predictor of 1-year mortality with a hazard ratio of 10.3 in trauma patients over 65 years old admitted to the intensive care unit.

Consequent to the strength adaptation using the variety of low load BFR interventions as noted above, BFR training has garnered increased attention in the rehabilitative and medical community as an intervention to treat persistent muscle weakness.[29,78–80] Early studies demonstrated enhanced muscle mass, strength, and increased walking speeds in elderly patients with muscle weakness.[32,34,35,37,41,81] Following this, a recent meta-analysis by Hughes et al,[82] showed a moderate effect when BFR was used as a rehabilitative intervention for knee osteoarthritis, elderly sarcopenic patients, ACL reconstructions and a patient with inclusion body myositis. These promising results have also been extrapolated by Hylden and colleagues who showed, in a small case series, that BFR exercise displayed dramatic increases in quadriceps peak torque, total work, and power in traumatically injured patients who failed traditional rehabilitative means when performing leg press, reverse leg press, and leg extension at 20% of each patient's single maximum repetition.[83] These early results have been repeated in unpublished data displaying large increases in quadriceps strength in postoperative patients who failed to recovery following a prolonged course of traditional physical therapy (Tennant, unpublished observations).

Several studies have established persistent weakness and debilitation following lower extremity fracture, total joint arthroplasty, and arthroscopy related surgeries.[65,84–87] With the goal of minimizing postoperative debility following lower extremity surgery, Tennent et al,[29] explored the efficacy and safety of BFR training in a randomized, controlled pilot study in those patients undergoing routine knee arthroscopy. This study showed a significant 2-fold comparative increase in quadriceps strength and improved functional outcome measures. Similarly, Ohta and colleagues observed significantly larger strength increases between weeks 2 and 16 in postoperative anterior cruciate ligament (ACL) patients who underwent rehabilitation incorporating BFR training than those who did not.[27] Another study evaluating BFR application training following ACL reconstruction using quadriceps size as a surrogate for strength, without objective strength testing, showed disuse muscle loss was mitigated relative to controls as measured by MRI imaging.[88] Each of these studies displayed adequate safety profiles without significant adverse events following the BFR training. Although further prospective comparative studies using patients at higher risk of developing persistent postoperative and postinjury weakness are ongoing,[89] these initial results are quite promising. An increase in similar findings might assist in decreasing the overall societal cost of general sarcopenia/dynapenia and postsurgical and traumatic debility while increasing overall functional outcomes and quality of life.

BFR IMPLEMENTATION IN OLDER ADULTS

Despite evidence supporting the efficacy of BFR in reducing the effects of sarcopenia, dynapenia, and assisting in a functional recovery following medical procedures, concerns about the safety of these exercise techniques remain. In 2006, Nakajima and colleagues distributed a survey to over 105 institutions using a BFR device to examine the incident rate of adverse events in a general exercise population. Participants ranged from ages below 19 to above 80 years and spent a total of 5 to 30 minutes under partial blood flow restriction. Researchers reported adverse events related to: discomfort, pain, and possible nerve damage (13% bruising at the site of the cuff, 1% numbness, and <1% cold feeling), vascular damage (< 1% cerebral anemia, <1% venous thrombus, <1% deterioration of ischemic heart disease, and <1% pulmonary embolism), and rhabdomyolysis (< 1%).[90] In addition, researchers have concerns regarding increased oxidative stress and slowing nerve conduction velocity.[91] However, after a 4-week study examining the safety of BFR using a pressure of 130% above resting systolic blood pressure, there were no differences in nerve conduction as measured by h-reflex.[92] In regard to oxidative stress, Godfarb and colleagues examined the plasma protein carbonyls, a marker of oxidative stress, among 3 groups: a group combining low intensity exercise with partial occlusion (30%1-RM), a group combining moderate intensity exercise with no occlusion (70%1-RM), and a group with exercise and only partial occlusion. They observed similar increases plasma protein carbonyls between the group with partial occlusion only and the moderate exercise group, but less oxidative stress with the addition of low-intensity exercise. Though the mechanism behind the reduction of plasma protein carbonyls with low-intensity exercise is unclear, the findings suggest that the oxidative stress response to BFR is similar to that of traditional resistance training.[93] Previous studies have examined the risk of cardiovascular dysfunction and deep vein thrombosis with the use of BFR exercise in elderly adults and

TABLE 1. BFR Exercise Device and Cuff Pressure Prescriptions in Older Adults

References	N	Age (y)	BFR Device	Cuff Pressure Prescription
BFR walking exercise				
Abe et al[32]	19	60-78	Kaatsu Master	Seated Kaatsu cycle at 100 mm Hg to training pressures 160-200 mm Hg (increased by 10 mm Hg per week).
Ozaki et al[35]	18	57-73	Kaatsu Master	Seated Kaatsu cycle at 120 mm Hg to training pressures 140-180 (increased by 10 mm Hg per week).
Ozaki et al[34]	23	57-76	Kaatsu Master	Seated Kaatsu cycle at 120 mm Hg to training pressures 140-200 (increased by 10 mm Hg per week).
Clarkson et al[44]	19	60-80	Zimmer Tourniquet System	60% of limb occlusion pressure while standing.
Iida et al[33]	16	59-78	Kaatsu Master	Seated Kaatsu cycle at 100 mm Hg to training pressures 140-200 mm Hg (increased by 10 mm Hg per week).
Body weight exercise				
Yokokawa et al[36]	44	65-79	M.P.S 700 (Kaatsu)	70 mm Hg up to 150 mm Hg (1.2 times systolic BP) (increased by 10 mm Hg per week).
BFR elastic band exercise				
Yasuda et al[37]	17	61-85	Kaatsu Master	Seated Kaatsu cycle at 30 mm Hg to training pressures to 120 mm Hg on day 1, increased by 10-20 mm Hg up to 270mm Hg, mean 196 ± 18 mm Hg.
Thiebaud et al[38]	16	~59	Kaatsu Master	Initial pressure 35-45 mm Hg increasing to 120 mm Hg.
BFR resistance exercise				
Vechin et al[30]	23	59-71	18 cm wide cuff DV-600	50% of the maximal tibial arterial pressure (mean 71 ± 9 mm Hg).
Karabulut et al[39]	37	50-64	Kaatsu Master	Initial pressure160 mm Hg then increased 2 20 mm Hg per session based RPE up to 240 mm Hg (mean 205.4 ± 4.3 mm Hg with RPE of 16.5 ± 0.5).
Shimizu et al[42]	40	> 65	Tourniquet 9000	Same cuff pressure as brachial systolic.
Patterson et al[41]	10	64-70	Hokanson rapid cuff inflator	110 mm Hg.

have reported no differences between groups in arterial stiffness or blood coagulation factors.[33–35,37,42,92] Some studies have found that BFR can safely improve cardiovascular health.[34,42] For example, increased arterial compliance was observed following treadmill walking with and without BFR with no differences in carotid or brachial blood pressure between groups.[34] Similarly, increased vascular endothelial health factor was observed following lower body resistance training with and without BFR.[42] Uniquely, increased leg venous compliance and maximal venous outflow were observed with BFR treadmill walking over a period of 6 weeks.[33] Overall, these studies have shown increases in leg girth, muscle cross-sectional area, strength, or functional ability indicating that BFR exercise combined with exercise may be a safe alternative to attenuate the loss of muscle function and possibly improve cardiovascular health in aging adults.

Though the risk of injury to the cardiovascular system appears to be low, BFR exercise may be associated with increased discomfort, pain, or the rare event of rhabdomyolysis. Studies recording the ratings of perceived exertion (RPE) have reported higher values for participants undergoing some form of BFR.[37,44] However, it should be noted that the RPE reported by Clarkson et al[44] was greater with BFR (11 vs. 8), but was reported as low and decreased as participants became more familiarized with the exercise. Similarly, participants completed a 4-week study in which they performed three sets of single-leg plantar flexion to failure, 3 times per week with an occlusion pressure of 110 mm Hg with no complaints and 100% compliance.[41] These findings imply that BFR exercise is tolerable as well as safe. Still, there is reason to be selective of participants as the risk of rhabdomyolysis and inflammation is low but serious. There have been 3 recent reports of rhabdomyolysis with BFR exercise[94–96] but the condition also occurs in more traditional resistance exercise methods.[97,98] Most recently, a case-study of a young woman (age 21) was reported who was diagnosed with exertional rhabdomyolysis following low-intensity exercise (without an inflated cuff) at an intensity (30% RM) that is similar to many BFR training studies.[99] Therefore, it is unclear if adding cuff inflation to exercise increases the risk of exertional rhabdomyolysis or not.[94] Until further research is done regarding the response of this condition to partial occlusion, it would be wise for clinicians to limit risk factors for exertional rhabdomyolysis including but not limited to: alcoholism, diagnosis of sickle cell anemia, heat intolerance, a history of deep vein thrombosis, those participating in extreme exercise regimens, drug use, and use of nutritional supplements containing ephedra or that may lead to dehydration.[100] Other studies examining markers of muscle damage and inflammation have reported no differences with occlusion.[24,40,92] Further, normal values of creatine kinase and interleukin-6 have been observed in both younger and older adults following 60 repetitions of BFR leg exercises.[24,40] Though events like increased oxidative stress and slowed nerve conduction may not be as concerning for young, healthy individuals, the effects in older adults is not well understood.[92,93] Nonetheless, researchers and practitioners should use caution

when prescribing BFR training to special populations and in the development of their exercise protocols.[94] The prescription of exercise may play a greater role in determining the safety of BFR exercise than age or activity level. A greater understanding of appropriate BFR exercise prescription progressions is also warranted. Table 1 summarizes how BFR exercise studies in older adults have prescribed exercise cuff pressure. Some studies follow a more progressive cuff pressure prescription, where subjects start low and increase the applied pressure gradually;[32–39] however, others have used a more standard pressure approach.[41,42,44]

In summary, as the United States society ages and as the incidence of musculoskeletal procedures correspondingly increases, improved rehabilitative interventions focused on minimizing sarcopenia, dynapenia, improving mobility, and preventing falls is required. Initial BFR exercise studies in older adults show promise as a potential clinically relevant intervention. BFR exercise can be combined with walking, body weight exercise, elastic band resistance exercise, and traditional resistance exercise. Furthermore, as the clinical adoption of this intervention continues, additional objective measures of its utility, limitations, and contraindications will become more readily apparent for the patient.

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Blood Flow Restriction Training in Rehabilitation Following Anterior Cruciate Ligament Reconstructive Surgery: A Review

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Summary: Anterior cruciate ligament (ACL) rupture is a highly prevalent orthopedic injury, resulting in substantial skeletal muscle atrophy because of changes in muscle protein balance and satellite cell abundance. Neural activation problems also contribute to strength loss, impacting upon a patients' physical function and rehabilitative capacity. Heavy loads typically required for muscle hypertrophy and strength adaptations are contraindicated because of graft strain and concomitant cartilage, meniscal, and bone pathologies associated with ACL reconstruction. Strength of the quadriceps is a fundamental component for the ability to reduce shearing and torsional strains on the ACL with ground contact, and forms a critical component of ACL rehabilitation. Given the dangers of early postoperative heavy-loading, low-load blood flow restriction (BFR) training may provide an alternative rehabilitation tool for practitioners. Passive BFR can attenuate early muscle atrophy and strength loss, and may be more effective with the addition of novel, complementary therapies such as neuromuscular electrical stimulation. Upon ambulation, aerobic, and resistance exercise with BFR can stimulate muscle hypertrophy and strength adaptations and resolve activation problems. This may occur through increasing muscle protein synthesis and satellite cell proliferation, decreasing muscle protein breakdown and improving muscle activation by altered recruitment patterns. Thus, BFR training may provide an effective rehabilitation tool that does not place heavy loads and force through the tibiofemoral joint. This may reduce the risk of damaging the graft, cartilage, meniscus, or other intra-articular structures, providing thorough screening before use is followed by correct, evidence-informed application.

Key Words: blood flow restriction—strength—rehabilitation—anterior cruciate ligament.

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The anterior cruciate ligament (ACL) is the most frequently injured knee ligament, with over 120,000 injuries occurring annually in the United States.[1] It is among the most commonly studied orthopedic injuries, thus the rehabilitation techniques used postsurgery have evolved over the last number of decades. Over this period practitioners have moved from their approach of minimal muscle activity and full immobilization to one of increased muscle activation and range of movement (ROM) in the early stages following surgery.[2–4] A major consequence of ACL injury and subsequent surgery is thigh muscle atrophy,[5] which contributes to thigh muscle weakness[6] in the first 12 weeks postsurgery[7] and can remain for over 2 years postoperation.[8] There are many short-term[9] and long-term[10] consequences of ACL surgery such as decreased protein turnover,[11] strength loss,[6] muscle activation problems,[12] an increased risk of osteoarthritis[13] and reinjury.[14] The effects of muscle atrophy are unavoidable given the reduced weight bearing and unloading context of ACL rehabilitation.[15] This is particularly evident postoperatively because of graft strains,[16] cartilage damage,[17] bone bruising and meniscal injury,[18] which serve as contraindications to heavy load exercise to regain muscle strength and size. Thus, clinicians are faced with the task of finding alternative rehabilitation tools.

Blood flow restriction (BFR) training has been proposed as a tool for early rehabilitation post-ACL surgery[19,20] because of its low-load nature and hypertrophic capacity.[21] Our recent meta-analysis indicated that low-load BFR training is a safe and effective clinical rehabilitation tool when applied correctly.[22] Despite limited published research to date,[19,20,23] to our knowledge there are several ongoing clinical ACL trials examining the use of BFR in rehabilitation. However, the various means by which BFR may affect the numerous consequences of ACL surgery have not been discussed in detail. Therefore, the purpose of this review is to examine the consequences of ACL reconstruction surgery, and discuss how BFR can be used to target specific aspects of the rehabilitation process.

CURRENT ISSUES AND CONSEQUENCES OF ACL RECONSTRUCTION

Muscle Atrophy and Strength Loss

Muscle atrophy and strength loss are major consequences of ACL injury.[5] An ACL-deficient or reconstructed tibiofemoral joint is depicted by decreased muscle strength and torque generating capacity,[24] which are attributed to muscle atrophy[25,26] and impaired muscle activation.[27,28] A most frequent finding is weakness of the quadriceps muscle group, in particular the vastus lateralis and medialis muscles.[29,30] A recent prospective case series examining lower limb muscle volume before and after ACL reconstruction surgery reported 15% atrophy in the vastus lateralis and rectus femoris compared with the contralateral, unaffected limb presurgery, and an excess of 20% in asymmetry in the vastus lateralis, medialis and intermedius and rectus femoris postsurgery.[5] In addition, anatomical changes of atrophy remained during early improvements in muscle activation and strength, and explain a large portion of weakness of the thigh muscles in the first 12 weeks postsurgery.[7] Quadriceps strength deficit can exceed a 20% loss of normal muscle strength 6 months after ACL reconstruction,[31] and such weakness can remain for over 2 years' postoperation.[8] Mounting evidence demonstrates

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that muscle weakness can be observed in the quadriceps muscles of asymptomatic patients who have returned to their normal, full preinjury activity levels after surgery[31,32] and such deficits can persist for years following reconstruction of the ACL.[33]

The quadriceps muscle groups extend the tibiofemoral joint, which is often restricted in terms of movement following ACL surgery to preserve the graft.[34] Weakness of this muscle group is disabling[24] and may contribute to more global dysfunction,[35] whereas also increasing the risk of reinjury[36] and early onset of osteoarthritis.[37] The loss of strength because of muscle atrophy and decreased muscle activation is unavoidable because of the necessary restrictions placed upon the postinjury and postsurgery recovery process, such as reduced load and weight bearing to ensure the graft is not over strained in the early stages of recovery. However, muscle atrophy and impaired voluntary force control negatively impact knee function following ACL surgery.[12] In addition, there are permanent anatomical changes associated with ACL reconstruction. For example, a recent study found changes in sonoelastographic strain ratio in medial distal femoral cartilage within the operated tibiofemoral joint,[38] which the authors suggested may indicate early structural changes following ACL reconstruction. These aspects all impact upon the patients' physical function, quality of life and their recovery process. To effectively combat the observed atrophy and strength loss following ACL reconstruction, and thus improve physical function and the rehabilitation process, it is important to understand the mechanisms of such changes.

Mechanisms of Muscle Atrophy and Strength Loss

The mechanisms underpinning the two defining aspects of strength loss, muscle atrophy[25,26] and decreased neural activation,[27,28] are well-documented. Atrophy of skeletal muscle, manifested as loss of muscle mass,[39] occurs in the early postoperative period of unloading[40] following ACL reconstruction surgery. The atrophy is observed in the affected limb and is because of intrinsic processes such as changes in muscle protein synthesis. There is a decline in muscle protein synthesis[41] and an increase in breakdown[42] which both likely contribute to changes in muscle protein balance and loss of muscle mass.[39] Significant muscle atrophy and strength loss alongside increases in muscle myostatin messenger ribonucleic acid (mRNA) expression and muscle atrophy F-box (MAFBx) mRNA expression, which are markers of muscle atrophy, have been observed after only 5 days of disuse.[43] This short period of disuse was also found to lower myofibrillar protein synthesis rates and induce anabolic resistance to protein ingestion.[11] Other aspects such as reduced mitochondrial function and gene expression[44] and reduced satellite cell proliferation[45] within the vastus medialis have been associated with muscle atrophy.

Loss of strength is typically of greater magnitude than the loss of muscle mass,[46] which is attributable to clinical deficits in voluntary activation following ACL surgery.[47] Such neuromuscular coordination deficits are typically both short-term and long-term[48] and can persist at 12 months postsurgery.[49] Moreover, diminished control of voluntary force capacity of the quadriceps impairs knee function.[12] Given the debilitating impact of loss of muscle strength on a patient's physical function and rehabilitative capacity, the primary aims of ACL rehabilitation are focused on regaining muscle size, strength, and preinjury activation levels to alleviate instability symptoms and restore normal physical functional activity.[50]

PRINCIPLES OF ACL REHABILITATION

The Primary Goals of ACL Rehabilitation

The principle goal of rehabilitation is to return an individual to normal function with a low risk of reinjury. The overall objective of ACL rehabilitation is to reduce the shearing and torsional strain through the ACL during activities of increasingly dynamic and complex nature[51] alongside tackling the deficit in muscle activation that is common following ACL surgery.[28,47,48] As the ACL is ruptured during activities which involve large knee abduction moments in short time frames[52] successful rehabilitation involves reducing the risk of this occurring in competitive scenarios.

To achieve this; the knee extensors and flexors and hip extensors must be strong enough to overcome the shearing forces at the knee associated with foot contact with the floor.[53] The hip abductors must be strong enough to overcome the torsional force at the knee associated with foot contact.[54] The coactivation synergies of the muscles around the knee and hip must be able to respond to the short time frames required to stabilize the knee during dynamic movement tasks,[49,55] and the kinematic strategy adopted during dynamic tasks must retain the center of mass over the center of pressure and reduce knee valgus to reduce strain and torsional loads associated with foot contact.[54] In addition, the neurophysiological and biomechanical demand is greater on an individual during reactive and unpredictable environments.[56]

Fundamental to these requirements, are the capabilities of the muscles of the knee and hip to produce an appropriate amount of force within a short period of time to overcome the magnitude and direction of forces associated with the ground contact period of sport specific tasks. Put simply, the muscles of the knee and hip must be strong enough to cope with the demands of the increasing forces that the individual will be subjected to when completing more demanding tasks. As strength is such a fundamental component of being able to reduce the shearing and torsional strains on the ACL during the demands of higher ground reaction forces associated with unpredicted changes of direction commonly found in sport, ensuring that an individual is strong enough is a critical component of an ACL rehabilitation program.

Why are Heavy Loads Contraindicated?

Developing muscle strength typically requires the repeated recruitment of high threshold motor units to induce the tissue strain or the physiological response required for an adaptive response.[57] In order to achieve this, training interventions typically demand volumes of work which require the muscles to produce $>65\%$ to 70% one repetition maximum (1RM).[58] However, there are a several contraindications to such heavy load exercise. Completing this intensity of work may produce strain loads which the recently reconstructed ACL is unable to tolerate.[34] Graft failure because of excess strain is a primary concern[59] across the 2 commonly used grafts to repair an ACL, bone-patellar tendon bone autograft[60] and the hamstring autograft.[61] Over-strain of the graft may result in an adverse response and prolong the duration of rehabilitation. Concomitant injuries after acute ACL tears are common,[18] including collateral ligament sprains, cartilage damage and meniscal pathologies.[62] In addition, subchondral bone lesions, or bone bruising, have been reported to occur in $>80\%$ of patients with a complete ACL rupture in the acute phase[63,64] and have been associated with meniscal tears.[65] Such pathologies associated with ACL tear and reconstruction reduce the load bearing

capacity of the tibiofemoral joint. However, equally the longer the muscle is inactive the more likely it is to atrophy[43] and be unable to produce the forces required to reduce the shearing and torsional strains associated with unpredicted changes of direction.[51]

To ensure successful ACL rehabilitation and reduce time scale of recovery, it seems logical to find ways to increase muscle strength and size without placing unwanted strain loads on the tibiofemoral joint. Blood flow restricted exercise could provide a convenient solution to this problem as the loads required to produce physiological adaptations in muscle strength and size are lower than traditionally used.[21] At present, no clear effect of BFR has been found proximal to the cuff, thus BFR may be most beneficial for rehabilitation of the muscles that control the tibiofemoral joint as opposed to the hip.

BLOOD FLOW RESTRICTION TRAINING

Overview of Application and Adaptations

The past 20 years has seen BFR exercise emerge as a novel method of training, with an extensive literature base. It involves restriction of blood flow to the working muscle by partial and full restriction of arterial and venous blood flow, respectively.[66] It is commonly applied to both lower and upper limbs using pneumatic tourniquets,[67] inflatable cuffs,[68] and elastic wraps.[69] Early research identified the capability of BFR to stimulate muscle hypertrophy and strength gains when combined with low-load resistance[70] and low-intensity aerobic[71] exercise. To date, a definitive mechanism(s) underpinning adaptations to low-load BFR training has not been pragmatically identified; however, several potential mechanisms have been proposed and reviewed in depth.[66,72,73] These proposed mechanisms include: cell swelling;[74] increased muscle fiber recruitment;[75] increased muscle protein synthesis[76] and increased corticomotor excitability.[77]

The low-load nature and hypertrophic capacity of BFR training identified its potential as a clinical rehabilitation tool; an alternative to heavy-load resistance training in populations that require muscle hypertrophy and strengths gains but in which heavy-loading of the musculoskeletal system is contraindicated.[21] Clinical research has demonstrated significant muscular adaptations in patients suffering from muscle atrophy and strength loss, including those with knee osteoarthritis,[78–80] sporadic inclusion body myositis,[81,82] older adults at risk of sarcopenia,[83,84] and ACL reconstruction patients.[19,20] Our recent meta-analysis examined the use of BFR training as a clinical rehabilitation tool, concluding that low-load BFR training was more effective at increasing muscle strength as opposed to low-load training alone, and may stimulate greater adaptations in muscle size and physical function during periods of rehabilitation.[22]

BFR in ACL Rehabilitation: Overview of the Current Evidence

Within the context of ACL injury rehabilitation there is great promise for the use of BFR training, both with and without low-load exercise. Following surgery there is often a short period of unloading, which results in atrophy.[5] Passive BFR (4 days postsurgery, 5 sets of 5 min BFR at 238 mm Hg for 10 days) has been used to attenuate knee flexor and extensor CSA decrease by approximately 50% compared with controls.[20] Following a period of unloading passive BFR was also found to compare more favorably to control and isometric exercise conditions at attenuating atrophy,[85] even at 50 mm Hg.[86] However, not all evidence is positive for this technique; one study found no attenuation of muscle atrophy following BFR or a control group in patients in the 2 weeks post-ACL surgery ($13.8 \pm 1.1\%$ vs. $13.1 \pm 1.0\%$, respectively).[23] As well as attenuation of atrophy by BFR per se, augmentation of low-load resistance training with BFR has also been shown to be effective in attenuating muscle mass loss and weakness. A prospective study in ACL reconstruction patients demonstrated greater increases in cross-sectional area (CSA) and muscular strength in the BFR group compared with a control group when implementing low-load muscular training with moderate BFR in the first 16 weeks postoperation.[19] This has also been evidenced in healthy subjects who underwent a low-load BFR training protocol (3 sets to failure at 20% of maximum voluntary contraction (MVC), 3 times per week) during 30 days of unilateral lower limb suspension (ULLS).[87] Furthermore, low-load BFR training has been used in a case study on an injured female athlete following ACL surgery.[88] Over a 12 week period the authors reported an increase in thigh size/girth of the affected limb and an increase in lower extremity functional scale (LEFS) scores compared with pre-surgery values.

This summary of current research that has examined BFR in ACL rehabilitation and periods of brief unloading and muscle disuse highlights its potential for use as a rehabilitation tool. Specifically, the low-load nature of BFR training may be critical in the early postoperative phase to increase quadriceps muscle strength, hypertrophy, endurance, and voluntary activation. This is without heavy loading of the tibiofemoral joint, thus allowing for preservation of the graft and reducing the risk of aggravating any concomitant cartilage, meniscal and bruising pathologies. Current, general BFR research suggests it may be used in a progressive model through all stages of rehabilitation from early postop to return to heavy load exercise[89] and pre-injury activity levels. The next section of this review will revisit this progressive model and discuss BFR application specific to ACL rehabilitation throughout each phase. It will examine how it may combat the mechanisms of muscle atrophy and strength loss previously discussed and update the model with more recent evidenced-based guidelines on safe and effective application.

BFR in ACL Rehabilitation: A Progressive Model

Phase 1: Early Postoperative with BFR

The primary goals of the early postop phase are reducing joint effusion, pain control and combating muscle atrophy and strength loss. As aforementioned, muscle atrophy during early postop unloading[39,40] is caused by a disturbance in muscle protein balance, namely a decrease in synthesis[41] and an increase in breakdown.[42] Passive BFR is thought to cause cell swelling that is evident after release of the cuff;[74] such acute cell swelling can stimulate protein synthesis and suppress breakdown,[90,91] which may stimulate the anabolic effects of BFR previously described.[74,85,86] Enhanced mammalian target of rapamycin (mTOR) signaling in a rat skeletal muscle model has also been demonstrated with passive BFR.[92]

BFR can be applied using a protocol of 5 sets of 5 minutes occlusion followed by 3 minutes of rest and reperfusion to attenuate muscle mass and strength of the quadriceps muscles.[85,86,93] In addition, voluntary isometric contractions during BFR may increase metabolic stress and cell swelling levels that may contribute to the hypertrophy process,[66,74] acting as a preparatory stepping stone to subsequent low-load rehabilitation. One study used a lower pressure,[86] but it was not

completely effective; it may be that full limb occlusive pressure (LOP) is required for passive BFR application in this stage. This should begin a few days postsurgery permitting that inflammation, pain and swelling is not excessive, and patients have passed a risk assessment questionnaire.[94]

Combining this with neuromuscular electrical stimulation (NMES), which is commonly used to combat muscle atrophy and strength loss following ACL surgery[29,95] and can prevent the decrease in muscle protein synthesis during unloading,[96,97] may have a greater effect in attenuating atrophy and strength loss. Although this is a novel concept, studies combining low-intensity NMES with BFR have found increases in muscle size and strength.[98,99] NMES of the quadriceps does not involve transmission of large forces through the tibiofemoral joint, thus exhibiting a low risk of damaging the graft or exacerbating any cartilage, meniscal, or bone injuries. Early increases in muscle strength and size are necessary to perform voluntary training later in the rehabilitation process,[100] and there is debate over whether passive BFR alone is truly effective.[23] Thus, we are proposing NMES with BFR as an updated and potentially more effective approach to the early postop phase. For an overview of optimal parameters for NMES, see Spector et al.[101]

Phase 2: Postoperative Ambulation With BFR

The primary goals of this phase are to further attenuate atrophy and strength loss, improve quadriceps activation and control, and normalize gait kinematics. Full knee extension is required to start gait reeducation;[94] if a patient starts to undertake high volumes of walking with a pathological gait pattern, there is opportunity for further injury or tissue overload of other structures supporting that movement pattern.[54] Providing patients have full ROM, BFR walking activities can help meet the goals of this phase.

Unloaded isotonic work acts as a prerequisite for regaining muscle strength and size during low-load resistance rehabilitation. Combining activities such as walking with BFR has been shown to increase muscle size and strength[71] and multiple aspects of physical function;[102] it may therefore be used to increase muscle size and strength in early ambulation post-ACL surgery. Once patients are able, cycling can also be combined with BFR; low-intensity cycling with BFR can concurrently increase muscle hypertrophy and aerobic capacity.[103] It may also promote muscle deoxygenation and metabolic strain, thus further stimulating endurance adaptations in the quadriceps to combat the postsurgery loss of muscular endurance.[104] BFR should be prescribed at a pressure between 40% and 80% LOP; aerobic exercise intensity is typically prescribed at a low percentage of VO_2 max or heart rate reserve, depending upon on the mode of exercise.

Phase 3: Low-load Resistance Training With BFR

Once patients have full range knee flexion and extension and gait is normalized, low-load resistance training is normally introduced. This is to accelerate the hypertrophy process and improve strength to begin a return to full weight bearing and preinjury activity levels. The strength and hypertrophy adaptations from low-load resistance training with BFR are well-documented,[105] with our recent review and meta-analysis concluding that low-load BFR training is an effective, tolerable and useful clinical MSK rehabilitation tool.[22] During this phase of the model, progressive and individualized low-load resistance training on 2 to 3 days per week using a low-load between 20% and 30% 1RM is sufficient for muscle size and strength adaptations,[22,66] using an occlusive pressure of 40% to 80% LOP.[106]

Low-load resistance training with BFR has been shown to increase muscle protein synthesis,[76,107] which may be a result of activation of the mTOR signaling pathway that is thought to be an important cellular mechanism for enhanced muscle protein synthesis with BFR exercise.[76,108] Such increases in muscle protein synthesis with low-loads can help recover and increase muscle size without loading the tibiofemoral joint with the heavy loads traditionally required for such an adaptation.[58] Low-load BFR resistance exercise may also be used to combat the reduced muscle satellite cell abundance observed during periods of unloading following ACL surgery.[45] Proliferation of myogenic stem cells and addition of myonuclei to human skeletal muscle, accompanied by substantial myofiber hypertrophy, has been demonstrated following 23 training sessions in just under 3 weeks.[109]

Regarding strength, the early preferential recruitment of type II fast-twitch fibers at low-loads because of the hypoxic muscular environment generated during BFR exercise is thought to be an important mechanism behind strength adaptations at such low loads.[73] With BFR exercise, it appears that the normal size principle of muscle recruitment[110] is reversed.[21] Fast-twitch fibers, which are more susceptible to atrophy and activation deficits during unloading[111] and are normally only recruited at high intensities of muscular work, are recruited earlier. Indeed, several studies have demonstrated increased muscle activation during low-load BFR resistance exercise.[112,113] Greater internal activation intensity has been found relative to external load during low-load BFR resistance exercise,[75,114] suggesting type II fibers are preferentially recruited. Such preferential recruitment of the fibers that are more susceptible to atrophy[111] during the early stages of ACL rehabilitation may help combat activation problems while also triggering muscle hypertrophy and recovery of strength.

Phase 4: Heavy-load Resistance Training With Low-load BFR Training

The end goal of ACL rehabilitation is for patients to be able to resume heavy loading and return to, or exceed, their preinjury strength and activity levels. Heavy-load resistance training is more effective at increasing muscle strength compared with low-load BFR training,[22] thus the latter may best be used as tool for effective and potentially quicker progression back to heavy exercise loads. Combination of low-intensity BFR resistance training with heavy-load training has been shown to increase muscle strength and size gains compared with low-load BFR training alone.[115] Once physically able, individuals can integrate low-load BFR training with high-load resistance training to reintroduce larger mechanical loads to structures of the MSK system. This can stimulate other adaptations alongside muscle size and strength, such as tendon stiffness—which may not be possible with low-load BFR training[116]—to contribute to further improvements in physical function. It is important that the patient is physically able to utilize the heavy loads required without an adverse reaction. Therefore, it is recommended that the patient should be able to exercise with the loads required to stimulate muscle and tendon adaptation of 65% to 70% preoperative 1RM[58] when entering this advanced phase of rehabilitation.

BFR and Other Aspects of ACL Rehabilitation: A Summary

Research regarding the effect of BFR on concomitant injuries with ACL rupture and reconstruction is less advanced. At present, BFR is thought to have limited or no effect on tendon stiffness,[116] likely because of its low-force nature, and

any intra-articular effects have yet to be pragmatically examined. One case study has shown an increase in serum bone alkaline phosphatase, a marker of bone formation, following low-load BFR resistance training in an individual suffering an osteochondral fracture,[117] suggesting BFR may have an impact on bone health. Further investigation of this may identify benefits for rehabilitating bone bruising following ACL rupture and reconstruction. Several clinical trials are proceeding, including one of our own, examining the effect of BFR during ACL rehabilitation. To our knowledge, trials examining the effect of BFR training following meniscus and articular cartilage repairs are underway. At our present situation, there is great potential with BFR training for increasing muscle hypertrophy, strength and combating muscle activation deficits following ACL surgery without overloading a recovering tibiofemoral joint and risk reversing the positive effects of the surgery, or worsening any concomitant pathologies.

SAFETY OF BFR TRAINING

Given the delicacy of ACL reconstruction, it is important that rehabilitation is approached in a safe yet effective manner.[22] Despite concerns of disturbed hemodynamics and ischemic reperfusion injury,[118,119] the safety of BFR training has been extensively reviewed[119,120] and reported to provide no greater risk than traditional heavy-load training.[121] Reports of rhabdomyolosis have occurred;[122,123] however, the cause was likely inappropriate and unclear prescription of BFR training.[22] However, BFR is safe if applied correctly—a recent questionnaire-based study demonstrated that there is a wide variety of protocols used[124] despite well-documented guidelines in the literature.[22] To further ensure safety, an extensive and thorough screening must take place before implementing BFR;[22] for an overview see Kacin et al,[120] Hughes et al,[22] and Patterson et al.[125]

CONCLUSIONS

Quadriceps muscle atrophy, strength loss, and activation deficits can be combated with low-load BFR training. Passive, aerobic, and low-load resistance training with BFR can stimulate adaptations in muscle size, strength, and endurance and improve muscle activation without heavy loading of the tibiofemoral joint. BFR may reverse the decline in muscle protein synthesis and increase in breakdown, and the decrease in satellite cell abundance observed during unloading following ACL surgery. It may also preferentially recruit muscle fibers that are more susceptible to atrophy at low-loads, which are not normally engaged with low load exercise. Thus, if BFR is applied safety and correctly, it can provide an effective and appropriate rehabilitation tool as the low-load nature places less strain on the graft and any cartilage, meniscal, and bruising injuries that are common with ACL rupture and reconstruction.

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Reported Side-effects and Safety Considerations for the Use of Blood Flow Restriction During Exercise in Practice and Research

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Summary: Blood flow restriction (BFR) exercise is seen as a potential alternative to traditional training methods, and evidence suggests this is being used with both healthy and clinical populations worldwide. Although the efficacy of the technique regarding muscular adaptations is well known, the safety of its use has been questioned. The purpose of this review was: (i) provide an overview of the known reported side-effects while using BFR exercise; (ii) highlight risks associated with the cardiovascular system, and; (iii) suggest recommendations to minimize risk of complications in both healthy and clinical populations. Overall, reported side-effects include perceptual type responses (ie, fainting, numbness, pain, and discomfort), delayed onset muscle soreness, and muscle damage. There may be heightened risk to the cardiovascular system, in particular increased blood pressure responses, thrombolytic events, and damage to the vasculature. However, while these may be of some concern there is no evidence to suggest that BFR exercise elevates the risk of complications any more than traditional exercise modes. Several modifiable extrinsic factors for risk minimization include selecting the appropriate BFR pressure and cuff width, as well as completion of a preexercise safety standard questionnaire to determine any contraindications to BFR or indeed the prescribed exercise. On the basis of the available evidence, we are confident that the side-effects of using BFR are minimal, and further minimized by the use of an appropriate method of application in the hands of a trained practitioner.

Key Words: KAATSU—safety—side-effects—vascular occlusion—exercise.

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Exercise training with blood flow restriction (BFR) is a technique whereby limb blood flow is reduced via external compression that is typically applied with a pneumatic cuff or tourniquet. More specifically, it is expected that BFR results in a partial restriction to arterial in-flow while occluding venous outflow. BFR is most commonly applied during resistance exercise,[1] and is seen as a potential alternative to traditional heavy-load resistance exercise (HLRE) [$\geq$70% 1 repetition maximum (1RM)] due to the light-loads prescribed (20% to 40% 1RM) that reduce the mechanical stress on the musculoskeletal system, while providing gains in muscle strength and mass that are greater than non-BFR equivalent intensity exercise, and on occasion have been reported to be similar to HLRE.[2–4]

The use of BFR in both healthy and clinical populations has seen a rise in popularity over the past 2 decades, with many of the original studies focusing on the efficacy of the use of BFR with respect to muscle adaptations and performance. More recently though, several papers have questioned the practicality and safety of BFR in some human populations.[5–13] However, it would be expected that many of the purported risks and/or side-effects may be avoided with well-controlled use of suitable equipment to induce BFR, and when in the hands of trained practitioners with knowledge of the technique.

To quantify the risk of BFR exercise for a specific population, it is important to compare the responses, side-effects, and any adverse complications with that of traditional resistance exercise with heavy-loads or light-loads, as well as high-intensity and low-intensity aerobic exercise as these are the current standards to improve muscle strength, mass, and endurance. As an example, some populations are contra-indicated to HLRE due to the risks associated with more extreme elevations in blood pressure (BP), and thus the added risk of a cardiovascular event.[14] Others may be contraindicated due to the mechanical strain placed on the musculoskeletal system while lifting heavy-loads, such as low physical functioning populations. Therefore, BFR exercise may be prescribed as an alternative exercise method for populations contraindicated to traditional modes, provided that BFR confers some benefit to the risk of elevated BP or provides benefit due to the use of light-loads.

Therefore, the purpose of this review is to provide an overview of the current literature associated with reported side-effects while using BFR. In addition, to discuss factors that may be considered important when examining the risks and contraindications of BFR. Lastly, we suggest several modifiable factors for risk minimization when using BFR in populations that are often contraindicated or those that may be at greater risk of adverse events during traditional modes of exercise.

REPORTED SIDE-EFFECTS WHILE PERFORMING BFR EXERCISE

There have been reports of side-effects as a result of performing BFR exercise. Even the original creator of the BFR technique (referred to as Kaatsu in Japan), acknowledged that he found it difficult to apply the appropriate pressure for himself and to other individuals during early experimentations, to a point where his skin would turn pale and he was later diagnosed with pulmonary embolism, although there is no evidence to suggest that this was caused by BFR.[15]

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As the technique was popularized in Japan, the largest epidemiological study of BFR usage demonstrated particularly low incidences of any adverse events for BFR exercise.[5] The most common reported side-effect was subcutaneous hemorrhage (13%) followed by numbness (1.3%), and with occasional reports of cerebral anemia, feeling cold, venous thrombus, pain, itch, and others. However, while some of these may be considered more serious adverse outcomes, there is no indication of any underlying medical conditions for those in the survey who suffered adverse events, and given the occurrence of these adverse outcomes was lower than the natural incidence across the broader population, it is difficult to conclude that these outcomes were a direct result of the BFR. However, it is known that at the time of the survey, in Japanese centers BFR was applied with relatively thin cuffs (~3 cm) and high pressures in excess of 160 to 200 mm Hg. As such, it is feasible that this implementation of BFR may have been more likely to produce adverse side-effects that are now rarely reported. A more recent global survey of practitioners and researchers that implement BFR in a wide variety of populations showed similar reported incidence of subcutaneous hemorrhage/bruising (13%) while numbness was more prevalent (19%). Again, there was little evidence to directly align these outcomes with BFR, and even less alignment with the method of BFR application (eg, BFR pressure and cuff width). We are confident that the side-effects of using BFR are minimal, and further minimized by appropriate methods of application in the hands of a trained practitioner.

Perceptual Type Responses

Fainting/Dizziness

One of the highest reported side-effects in a recent survey of practitioners using the BFR technique was numbness and fainting/dizziness, with almost 20% of respondents declaring that they had observed this in their facility.[1] However, these were only reported in <1% of cases by Nakajima and colleagues, and it is likely these reported incidences inflate the true representation of these side-effects given there are no data on the number of users/participants of BFR within each facility, and does not account for overlap between practitioners in the survey that encountered the same event. In any case, it is likely these participants experienced postexercise hypotension, or even a vaso-vagal response associated with the application of BFR and so is expected to be a somewhat random incidence rather than being clearly definable, identifiable, and predictable in particular participants.

Numbness

The first randomized control trial to comment on a sensation of numbness in the quadriceps muscle during BFR exercise used high pressures (230 mm Hg) combined with wide cuffs (13 cm).[16] These are important factors to consider, given that the BFR pressure, duration of inflation, and cuff width are all modifiable prescription variables that may reduce the risk of these adverse responses. It is worth noting that numbness with BFR likely occurs either due to pressure applied to peripheral nerves, or more likely the development of ischemia in response to the restriction to flow.[17] In 1 study, sensory motor nerve conduction was not altered following 4 weeks of lower body resistance exercise with BFR,[18] which is not surprising given that BFR is typically only held for relatively short durations of 5 to 20 minutes. Even with experiments in which complete occlusion is induced for upwards of 30 minutes, these do not result in any long-term adverse effects or maladaptations and these side-effects are rapidly reversed following the removal of the BFR.[17] In addition, being transient events without long-term concerns, we do not expect these to be prohibitive for the prescription of BFR when using an appropriate method and in the hands of a trained practitioner.

Ratings of Perceived Exertion, Pain, and Discomfort

Most often BFR presents greater ratings of perceived exertion (RPE), pain, and discomfort despite the use of light-load resistance exercise (20% to 40% 1RM).[19–21] As such, one might suggest that BFR remains unsuitable for populations with low conditioning, poor motivation, and reduced adherence to exercise programs. However, for these population, most forms of exercise at least present with greater RPE. Therefore, if undertaking structured exercise, BFR should form part of the available repertoire. Indeed we have shown in older adults that RPE was great in the initial stages of a BFR walking training program, but this subsided over the first few sessions to be equivalent to that for non-BFR walking training.[22]

Importantly, some studies have shown that perceived exertion and pain are lower with BFR exercise in comparison with HLRE.[23,24] However, this seems to be a contentious area within the BFR literature with some opposing reports that are likely due to different exercise protocols and BFR methodologies used between studies.[19,21,25] Nevertheless, with these perceptual responses subsiding after a few exercise sessions with BFR,[20,26] there appears an adaptive effect on these perceptual responses that facilitates greater tolerance to BFR exercise once participants gain some familiarity with the experience.

Delayed Onset Muscle Soreness

Delayed onset muscle soreness (DOMS) seems to be commonly reported following BFR exercise, and can persist for 24,[27] 48,[28] and even 72 hours postexercise[24] depending on the exercise protocol and BFR methodology being used. BFR exercise has been shown to result in greater DOMS in comparison with exercise with the same loads without BFR,[24,27] whereas only 1 study has compared this response to HLRE and found the DOMS response to be greater with BFR.[24]

It is imperative to note that an episode of DOMS is relatively normal following unaccustomed exercise bouts, or due to higher than expected increases in exercise intensity (ie, external load) or volume (ie, total exercise volume).[29] So while the DOMS response peaks between 24 and 72 hours postexercise, this is a transient response to the exercise stimulus and not to BFR per se, before muscle soreness levels return to resting levels.

Markers of Muscle Damage

Given that DOMS is often associated with several markers of exercise-induced muscle damage, several different measures for muscle damage have been examined following BFR exercise. These are often measured as a time course response postexercise in comparison with resting measurements. Overall, the affiliated markers of muscle damage appear only slightly increased and/or rapidly return to resting levels. For example, maximal voluntary contractile force is reduced immediately postexercise[30] and at 24 hours postexercise,[27,31] whereas changes in muscle swelling, circumference, and range of motion all return to baseline levels within 24 hours of exercise completion.[28] Furthermore, although blood markers of muscle damage have not been extensively examined, creatine kinase, myoglobin, and interleukin-6 are not elevated following BFR exercise in both young and older healthy adults.[32–34] Given that

these observed markers are relatively low, it would appear that the BFR exercise confers no more risk for muscle damage (and perhaps even less so) than traditional training methods.

Of note, 1 paper observed reduced quadriceps muscle cross-sectional area at the site of muscle origin following BFR training.[16] However, this was likely due to the application of wide cuffs in combination with suprasystolic restriction pressures (230 mm Hg) resulting in high compression and shear stress to the tissue under the cuff. There have also been case study reports of BFR-inducing rhabdomyolysis,[35,36] which is a condition in which damaged skeletal muscle breaks down rapidly and myoglobin is released into the circulation. The patient in the first reported case study presented to hospital with elevated creatine kinase levels following just a single bout of BFR knee extension exercise. However, this patient was discharged from hospital after 3 days, and 18 days after the incident continued BFR exercise without further (reported) incident. The patient in the more recent case study[36] was a 30-year-old overweight man (body mass index, 28.1 kg/m^2) diagnosed with rhabdomyolysis within 24 hours following a single BFR exercise session. This was the first training session after a period of inactivity. Physical inactivity, and the early introduction of squats to a training program, which he performed with a BFR (pressure and load not listed), are both considered risk factors for rhabdomyolysis.[37] In addition, before any diagnosis of rhabdomyolysis, a high fever and pharyngeal pain (diagnosed as tonsillitis) were reported after the session and resulted in a local clinic prescribing a number of medications, which may have further promoted the later onset/diagnosis and treatment of rhabdomyolysis.[38] Therefore, this case of rhabdomyolysis seems to be more a result of a combination of factors, and probably not a result of the BFR. The large epidemiological study conducted by Nakajima and colleagues reported only 1 of 12,642 persons diagnosed with rhabdomyolysis following BFR exercise. More recently, of 115 practitioners surveyed in a questionnaire using BFR with their clients/patients, 3% reported an incident of rhabdomyolysis while using BFR.[1] However, 1 potential limitation of these studies is that it is not clear how rhabdomyolysis was determined, while a large range of populations with possible contraindications to exercise/BFR were captured, making it difficult to relate the adverse effects to BFR when so few occurrences have been noted. Overall, muscle damage seems to be a minor risk following BFR exercise.

Other Reported Side-Effects

There have been few other side-effects described in the current literature, but case studies have reported acute loss of vision,[39] and a series of complications including brain hemorrhage, petechial hemorrhage, and venous injury.[40] Although future studies are encouraged to report any side-effects that may occur during BFR exercise, it is somewhat difficult to elucidate if the complication was caused solely by BFR, the exercise stimulus, or via any underlying complicating physiology/pathology. Furthermore, the potential risk of using BFR either with or without exercise, and frequency of side-effects, should not be any higher than what is typically seen following traditional resistance or aerobic exercise.

POTENTIAL RISKS WHEN USING BFR DURING EXERCISE

Before prescription of any traditional mode of exercise, consideration is needed with regard to the potential risks of adverse events. This is typically undertaken through standard screening procedures to evaluate certain risks. Factors such as age, training history/habits, evidence of chronic disease (diabetes, hypertension, obesity, etc.), genetic/family medical history, current/prior musculoskeletal injury, etc., all play a role. However, often the focus is largely on BP and the associated complications that may arise as a result, and which vary between populations. These factors inform the practitioner of the risk of prescription of HLRE as well as intense aerobic exercise, yet despite BFR exercise prescribing the use of light-loads, similar considerations must be given these common contraindicators that confer added risk of adverse events to undertaking any exercise type. Therefore, in the sections below, we describe and discuss some of the potential contraindicators to BFR exercise to characterize their significance in the context of HLRE, given HLRE is considered the most likely exercise type to confer a significant risk of an adverse event. In addition, we review some other areas of focus that have previously been raised as a concern when considering prescription of BFR exercise.

Hemodynamics

For resistance exercise, the BP response increases in line with the resistance load, volume, and mass of skeletal muscle recruited for the action. Although this is normal for any exercise, BP may be exacerbated during HLRE with maximal values for mean arterial pressure being reported upwards of 250 mm Hg.[41] As such, BFR with light-loads is seen as a potential alternative.

A large body of the current literature has focused on the acute hemodynamic responses to BFR, both with and without exercise, and a systematic review of these responses was published recently.[42] It seems that when matched for the same external load (% 1RM) and total exercise volume (sets×repetitions), BFR resistance exercise typically elicits slightly higher acute increases in heart rate (HR), BPs, and cardiac output, with reductions in stroke volume, in comparison with non-BFR exercise.[23,43–47] However, when exercise is performed until muscle failure, these acute hemodynamic responses are similar between light-load BFR and non-BFR exercise.[16,48] The mode of exercise is also important to note, with BFR walking producing comparably lower elevations in BPs, HR, and cardiac output in comparison with BFR resistance exercise in both healthy young and older populations.[23,43]

Comparisons with heavy-load exercise are less frequent but in the context of risk assessment, probably the most important. Nevertheless, the hemodynamic responses with BFR exercise are generally shown to be similar,[23,44] and in some cases lower than for HLRE.[47,48] For example, evidence from our laboratory with both young and older healthy populations has shown that HR, BP, and cardiac output responses are similar to HLRE when utilizing high-pressure BFR exercise (~150 mm Hg), yet more similar to light-load resistance exercise when the BFR pressure is reduced (~90 mm Hg).[44] Myocardial workload (measured as the product of HR and BP) is also lower with BFR exercise in comparison with HLRE[49] or at least not any greater than traditional HLRE.[44,47] This is especially important to consider, given that increased muscle strength and mass may be derived though BFR exercise in conjunction with a reduction in exercising hemodynamic stress, and so may alleviate some of the risk associated with HLRE for populations that may be contraindicated.

Vasculature

There is growing interest in the effect of BFR exercise on vascular function.[48,50–57] In particular with respect to muscular

endurance, with current evidence suggesting that BFR exercise promotes postexercise blood flow, oxygen delivery, and capillarization (angiogenesis), resulting in an overall improvement in microvascular function.[53,58] The main stimuli for inducing skeletal muscle angiogenesis include intramuscular hypoxia, changes in vascular wall tension/shear stress, and mechanical overload produced during muscle contraction. The result is an increase in expression of several angiogenic factors. However, despite the low mechanical tension associated with BFR exercise in comparison with HLRE, results from a study by Larkin et al[59] showed that BFR exercise also increases the expression of several angiogenic factors, including vascular endothelial growth factor, hypoxia-inducible factor-1 α, and neuronal-nitric oxide synthase. Importantly, these responses were shown to be elevated immediately postexercise and up to 24 hours postexercise, which is similar to observations seen following HLRE[60] and early BFR research.[61] However, BFR exercise training [4 weeks of knee extension; with BFR (30% 1RM) or without (80% 1RM)] has not demonstrated any effect on measures of pulse wave velocity in healthy young adults,[18] and so this needs further investigation.

This potential effect of BFR on vascular function may prove particularly beneficial in populations that are more susceptible to endothelial dysfunction as a result of progressive atherosclerosis across the lifespan (eg, older adults). However, this raises some degree of caution given that BFR is more likely to produce turbulent arterial flow that can lead to vascular damage, thus placing populations like older adults at greater risk of a vascular event during BFR.[9,62] Although, recent evidence has demonstrated a positive effect on vascular endothelial function and peripheral blood circulation in healthy older adults without any reported contraindications.[57] Again, there is little evidence to support BFR being any more deleterious in populations susceptible to vascular injury, but provides an element of concern and certainly an area for future research.[9,62]

Thrombolytic Events

Given the nature of the application of BFR, there may be a concern associated with obstruction of blood flow producing conditions that may promote coagulation at sites of vascular damage and atherosclerosis. Fortunately, as mentioned above, there have yet to be any reports of deleterious effects of BFR on the vasculature within well-designed research studies. The epidemiological questionnaire conducted by Nakajima et al[5] reported thrombolytic complications at 0.055% (7 cases) in their large study sample, whereas only 0.8% of practitioners reported thrombolytic events with their clients in a more recent questionnaire, although the health and age of these participants was not able to be determined.

One way to measure the effect of BFR exercise on thrombolytic events is by examining the acute and training-related changes in blood markers for coagulation (eg, fibrinogen and D-dimer). Nakajima et al[63] were the first to show that BFR resistance exercise did not alter prothrombin time or markers of coagulation, whereas Madarame et al[64] also showed that blood markers of thrombus formation and thrombin production are not elevated following a single bout of 4 sets of leg press with BFR. Similar results were found in a follow-up study by the same authors in patients with stable ischemic heart disease who were not currently treated with anticoagulant drugs.[65] Although these studies examined the effects of BFR following a single training session, Clark et al[18] did not observe any acute changes in fibrinolytic or coagulation markers following an initial exercise session with either BFR or heavy-loads, or following the final training session after 4 weeks of training in healthy young adults. This seems to be similar in healthy older adults (60 y and above), with 12 weeks of BFR resistance exercise of both the lower-body[66] and upper-body[67] showing no deleterious changes in coagulation factors such as fibrinogen degradation product or D-Dimer.

In contrast to the negatively associated effects of BFR exercise on thrombus formation, it would appear that resistance exercise without BFR[68] as well as BFR without exercise[69] have been shown to stimulate the fibrinolytic system. Importantly as well, the combination of BFR and light-load resistance exercise helps to promote a fibrinolytic state,[63,64] which inhibits thrombus formation. Therefore, while most of the aforementioned studies were conducted in healthy populations, it would appear that BFR exercise does not activate the coagulation system.

MINIMIZING RISK FACTORS WHEN PRESCRIBING BFR

There are several intrinsic and extrinsic factors that should be considered before conducting BFR exercise. Intrinsic factors can include an individuals' medical history, and are considered contraindications to BFR exercise (Table 1). These are somewhat less modifiable than extrinsic factors. Other intrinsic factors that are not contraindicators but should be considered before prescription of BFR exercise can include age, lifestyle

TABLE 1. Possible Contraindications to Use of BFR

Cardiovascular disease
Coronary heart disease
Unstable hypertension
Peripheral vascular disease
Venous thromboembolism
Hypercoagulable states (blood clotting disorders)
Cardiopulmonary conditions
Atherosclerotic vessels causing poor blood circulation
Silent myocardial ischemia
Left ventricular dysfunction
Hemophilia
Vascular endothelial dysfunction
Varicose veins
Induration/Marfan syndrome
Musculoskeletal injury
Recent muscle trauma or crush injuries
Postsurgical excess swelling
Open fractures
Open soft tissue injuries
Skin graft
Lifestyle
Age
Smoking
Body mass (eg, obesity)
Pregnancy
Uncontrolled diabetes mellitus
Dyslipidemia
Dehydration
Family medical history
Clotting disorders
Sickle cell anemia
Atrial fibrillation or heart failure
Cancer
Medications
Those known to increase blood clotting risk

On the basis of authors review of the literature and in consultation with medical professionals.

BFR indicates blood flow restriction.

factors, blood vessel size, limb size, muscle and adipose tissue thickness, and current strength capacity.[15] As such, the modification of extrinsic factors such as the final BFR pressure, duration of applied pressure, and the width of the cuffs or tourniquets is required to prescribe BFR exercise in an effective and safe manner.

Considerations on Patient Selection and Possible Contraindications

The majority of data available on healthy young populations suggests that BFR is a safe alternative to traditional modes of exercise; however, possible contraindications to the use of BFR are listed in Table 1. Over the past decade there has been an increase in adoption of BFR exercise in clinical populations such as older adults at risk of sarcopenia,[67,70] pregnant women,[71] following musculoskeletal injury,[72] patients with metabolic syndrome,[73] hypertension,[74–76] cardiovascular disease,[65,77] as well as obese clients.[78] Importantly, no adverse risk responses have been reported in published randomized control trials in these clinical populations, and while there have been some reported side-effects to BFR, it remains difficult to suggest whether BFR should be avoided in any special populations.

All populations should be assessed for possible risks and contraindications before performing BFR in research and practice. Therefore, thorough clinical judgement is required by the practitioner to determine if the individual is an appropriate candidate to perform BFR. For all research studies involving BFR (either with or without exercise), approval from the Institutional Research Review Board and signed informed consent from the study participants should be obtained. Although it may not be necessary for the lead investigator of a BFR research study to be a licensed physician, it would be expected that this person should be an expert in BFR with knowledge about principles, physiology, prescription, and potential side-effects or adverse reactions to the technique. In addition, it should be essential that before any use of BFR in research or the field that a standard prequestionnaire screen should be completed by all BFR candidates. An easy to use risk assessment tool was recently published.[10]

Providing that screening is administered, and the researcher/practitioner has knowledge of BFR and its application, there is potential for the use of BFR with broader clinical populations, provided the researcher/practitioner is well-versed in exercise responses in those populations or protocols are devised with a collaborator that is. For example, while uncontrolled hypertension may prohibit BFR use in the same way it prohibits HLRE, those medicated for hypertension may still be eligible for BFR exercise given that BP and BP responses may still fall within "normal" ranges seen during and following exercise.[79] Diabetes is often strongly associated with hypertension, and additionally requires strict monitoring of blood glucose.[80] However, both factors are easily measured and controlled by medication, meaning BFR exercise may not be contraindicated provided BP and blood glucose are monitored. Diabetes may still be contraindicated to BFR in the presence of symptomatic neuropathy or active retinal hemorrhage.[80] Thiebaud et al[81] highlighted the potential benefits of BFR exercise for chronic obstructive pulmonary disorder. Providing considerations to underlying cardiovascular concerns are well managed, and the prescription accounts for impaired respiratory capacity, BFR may be valuable for chronic obstructive pulmonary disorder. Pilot data (Stuart A Warmington and Matthew J Clarkson; Data collected, 2016) from our research group indicates that BFR applied during cycling exercise is appropriate for patients on hemodialysis. Neither BP, HR, nor dialysis adequacy were affected with low-to-moderate intensity BFR cycling compared with equivalent intensity non-BFR cycling, which is already a recommended prescription for dialysis patients.[82] Although these suggestions represent a range of clinical populations that may benefit from BFR with additional considerations, it is by no means a comprehensive list, and for most conditions further research is still required to confirm the suitability of prescribing BFR exercise.

BFR Recommendations for Practitioners and Research

It seems that the area of main concern regarding the use of BFR relates to the equipment being used (in particular the width of the restrictive cuff) and the final BFR pressure used during exercise and how this may initially be determined. Early research studies (eg, between 1998 and 2012) often prescribed arbitrary and excessive BFR pressures. However, this method is limited in that it does not account for interindividual differences in limb size (ie, both muscle and adipose tissue content), vascularization, and BP, which may not only decrease the efficacy of BFR with regard to functional adaptations, but may also be a safety concern if prescribed exercise pressures are excessive. The major focus for prescribing a pressure during BFR exercise should be to find the lowest possible pressure that remains effective for the individual. Loenneke et al[83] first proposed a standardization method to account for interindividual differences when using BFR. It was suggested that the pressure that produces a complete cessation of arterial blood flow, or the individual arterial occlusion pressure (AOP) be determined using Doppler Ultrasound at rest, and practitioners are encouraged to use a set percentage of that measurement for the BFR pressure.[84] Methodology for determining the AOP using Doppler Ultrasound has been provided previously,[85] whereas other devices utilize in-built technology to similarly determine the maximal limb occlusion pressure (LOP). Importantly, time of day also has an effect on the maximal AOP, thus practitioners should endeavor to measurement of AOP immediately before undertaking BFR exercise, or at least at the same time of day as previous measurements of AOP.[86] Furthermore, given that pressure transmission from the cuff to the underlying tissue is dependent on cuff width (discussed below), the cuff width used to determine AOP must be the same as that used to restrict blood flow during a BFR exercise bout.

Following on from the determination of AOP, the practitioner must decide what percentage of AOP to prescribe for the BFR user. The final restriction pressure used has varied widely (50 to 300 mm Hg) depending on the individual and exercising limb. However, similar increases in elbow flexion muscle strength, mass, and endurance have been observed between BFR pressures equal to 40% AOP (53 ± 7 mm Hg) and 90% AOP (116 ± 17 mm Hg), suggesting that lower pressures could be useful to avoid any deleterious responses to higher pressures.[87] There still is no consensus within the literature as to the most optimal BFR pressure, and utilization of AOP/LOP methods for BFR exercise is still low (11.5% of 115 surveyed practitioners).[1] In addition, it is unknown whether different BFR pressures may be required for prescription in different populations. For example, athletes versus nonathletes, older adults versus young adults, and a host of other populations. As such, despite limited information on safe yet effective BFR pressure prescription, we recommend use of a BFR pressure in the range of 40% to 80% AOP for both the upper-body and lower-body, with lower pressures perhaps just as efficacious as higher pressures while minimizing the risk of contraindications to BFR during exercise. It may also be prudent to begin training

programs at lower percentages and progressively increase the restriction pressure each exercise session while monitoring physiological and perceptual responses.

Restrictive cuffs can range from 3 to ≥15 cm in width. However, wider cuffs likely occlude arterial blood flow at lower overall pressures in comparison with narrow cuffs.[88,89] When using the same percentage of maximal AOP (80%), no differences in muscle strength or mass were observed following 12 weeks of training with either wide (10 cm) or narrow (5 cm) cuffs.[90] However, when matched for the same relative pressure (determined as a percentage of systolic BP), wider cuffs have been shown to induce a greater cardiovascular response in comparison with narrow cuffs,[91] and this may be seen as a potential concern, particularly for those with underlying cardiovascular issues. Overall, wide cuffs (8 to 10 cm for upper-body, 10 to 14 cm for lower-body) should provide a more effective transmission of pressure through the underlying tissue and vasculature in comparison with narrow cuffs (5 and 3 cm for upper-body and lower-body, respectively), and thus lower relative restriction pressures can be prescribed. It may be more likely that narrow cuffs and subsequently higher restriction pressures increase the risk of adverse responses in bruising, nerve compression, and numbness. Finally, contoured cuffs induce occlusion at lower pressures than commonly used straight cuffs.[92] As such, this should also be considered when prescribing BFR pressures.

BFR AND ORTHOPEDIC CONSIDERATIONS

The majority of the BFR-published literature has been conducted on nonclinical populations. However, clinicians have begun to apply BFR as part of a rehabilitation program after injuries and orthopedic surgery.[72] A number of published studies have assessed the effects of BFR after anterior cruciate ligament reconstruction without adverse events.[93,94] Time frames ranged from days 3 to 14 and weeks 2 to 16 postoperative. One trial included measurements of joint laxity via knee ligament arthrometry (KT2000) and found no significant difference between groups. The potential for thrombus formation has only been assessed in 1 postoperative BFR trial. In that study, 6 weeks of BFR after knee arthroscopy found no signs of thrombus formation on Duplex Ultrasound imaging.[95]

Currently, there are registered orthopedic trials assessing the effects of BFR after joint arthroplasty, anterior cruciate ligament surgery, femur fractures, and wrist fractures.[96] As more large robust clinical trials are completed the safety of BFR and appropriate clinical populations will be better understood. Orthopedic surgeons have adopted the use of surgical grade medical tourniquets in the operating room with minimal complications. In the clinical setting, applying BFR following the same safety principals utilized during surgery may help reduce potential tourniquet complications.[97]

CONCLUSIONS

The purpose of this review was to briefly discuss the reported side-effects of performing BFR either with healthy or clinical populations, to present some possible contraindications to BFR exercise, and to provide recommendations to minimize risk when using BFR in populations that are often contraindicated or those that may be at greater risk of adverse events during traditional modes of exercise.

On the basis of the current literature, it seems that BFR exercise can be used safely in most populations without significant risk of complications, provided that BFR is prescribed by trained practitioners that have knowledge of appropriate protocols (ie, restriction pressure application and durations, and their interaction with different cuff widths), and the possible contraindications to the use of occlusive stimuli. It is recommended that the final restriction pressures used during exercise should be calculated as a percentage of each individual's maximal AOP, with lower pressures (ie, 40% to 80% AOP) perhaps conferring a reduction in risk, making BFR safer and just as efficacious as higher pressures for improving musculoskeletal mass and strength, cardiovascular fitness, and functional abilities. The current data examining the safety aspect of BFR is in its relative infancy, although tourniquet safety has long been examined. Therefore, before performing BFR it is recommended that practitioners use a preexercise safety standard questionnaire that accounts for listed contraindications to BFR exercise (as well as traditional exercise modes) to determine any contraindications, and future studies should report and discuss any side-effects observed when using BFR exercise to improve our understanding of any arising issues with respect to safety.

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Software for Planning Precise Intraoperative Correction of Rotational Deformity of Extremity

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Summary: Most of the torsional deformities of the limbs correct spontaneously with growth. Corrective derotation osteotomy forms the mainstay of treatment for symptomatic residual deformities. The described techniques for calculation of intraoperative assessment of rotational correction involve approximation of calculations and measures. We have designed a new method of computation with minimal error. For derotation osteotomy of subtrochanteric region of femur, preoperatively, the magnitude of rotational correction of the femur is measured by computed tomography. The cross section of femur at subtrochanteric level resembles closely to a circle or ellipse. Following osteotomy, the major and minor axis are measured. The magnitude of correction will correspond to the arc length of the circle/ellipse. The calculation carried out by numerical integration using Python programming language. Once the arc length is obtained, the osteotomy is fixed with the desired implant. Postoperative computed tomographic scan is performed to assess rotational correction. Unlike previously described techniques, our study provides the closest possible approximation in intraoperative calculation of rotational correction of torsional deformity of any long bone. We believe that this technique would yield more accurate results thus averting possibility second surgery. Further studies are required to validate its accuracy in clinical use.

Key Words: rotational deformity—derotation—osteotomy—software—formula—calculation—elliptic integral.

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Torsional deformity of the lower limb is one of the common causes of gait abnormality in children. Most of this deformity corrects spontaneously with growth.[1] Corrective derotation osteotomy forms the mainstay of treatment for symptomatic residual deformities. Rotational osteotomy is performed as a standalone procedure or as an adjunct to varus and/or shortening osteotomy as in disease, hip dysplasia, or posttraumatic sequel. Under or over correction in these cases can lead to inadequate head coverage or in-toeing or out-toeing gait and thus repeat surgery. Hence, accurate calculation of the rotational component is prudent. A few techniques have been mentioned in literature for calculating the magnitude of derotation intraoperatively. However, these techniques are cumbersome and involve approximation of femoral measurements. We have designed a new method to calculate this magnitude of correction with minimal error.

TECHNIQUES

The formula is applicable for transverse rotational osteotomy of any bone, the cross section of which closely resembles a circle or an ellipse, that is, femur and tibia.[2] Below, we describe the method for derotation osteotomy of the subtrochanteric region of femur, this being a frequent site for derotation osteotomy in isolation or that in combination with varus-valgus osteotomies.

Preoperatively, the magnitude of rotational correction of the femur is assessed clinically and calculated by computed tomographic scan of the desired extremity. Following exposure of the subtrochanteric region, the osteotomy site is marked with an oscillating saw. The minimum anteroposterior width (minor axis) is measured at this level with bone calipers or bone holding forceps. The anterior point of the minor axis is marked and a 5 cm longitudinal ridge is etched, parallel to the femoral shaft with a wide oscillating saw and demarcated with methylene blue. The mediolateral width is now measured in a plane perpendicular to the measured AP width of the femur, at the

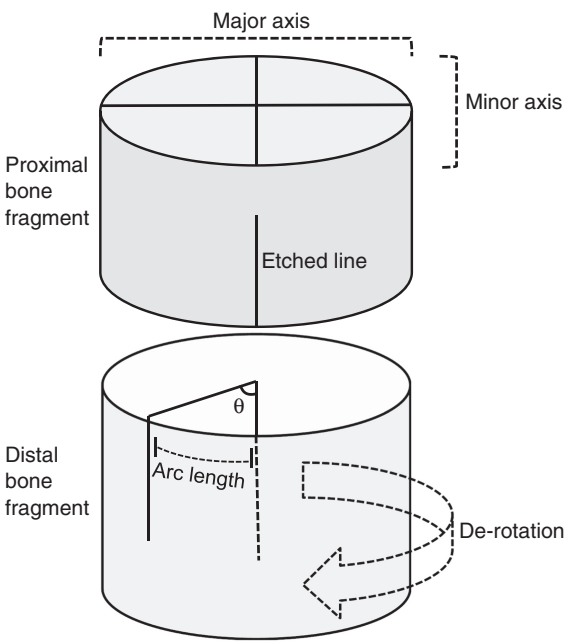

FIGURE 1. The diagram depicts derotation osteotomy of any long bone with minor axis as the shortest anteroposterior width, major axis as longest mediolateral width, and "θ" as the desired angle of correction.

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The authors declare that they have nothing to disclose.

For reprint requests, or additional information and guidance on the techniques described in the article, please contact Sangeet Gangadharan, MBBS, DNB (Orth), Fellowship Pediatric Orth, at drsangeetgangadharan@gmail.com or by mail at 1303, Varuna B wing, Dosti Vihar, Vartak Nagar, Thane west, Maharashtra 400606, India. You may inquire whether the author(s) will agree to phone conferences and/or visits regarding these techniques.

TABLE 1. Steps for Femoral Derotation Osteotomy

Mark osteotomy level
Measure minimum AP width (minor axis)
Etch longitudinal line over anterior point of AP measurement
Measure mediolateral width (major axis), perpendicular to AP width
Enter both measurements and angle of correction in the software
Obtain arc length
Displace bony fragments according to arc length
Fix osteotomy with implant
(In all cases, the shorter measure should be entered as minor axis)

AP indicates anteroposterior.

level of osteotomy. An osteotomy is centered perpendicular to the etched line, dividing it into 2 segments. The cross section of femur at the subtrochanteric level resembles closely to a circle in patients below 9 years and to an ellipse in those above 9 years of age.[2,3] The distal segment is medially or laterally based on the direction of correction. The displacement of distal segment in relation to proximal segment corresponds to the "arc length" of the circle/ellipse (Fig. 1). A formula to calculate arc length was integrated into a software. This formula can be applied to a circle as well as an ellipse. The measured anteroposterior and mediolateral lengths are entered in the software, the longer measure being the major axis, the lesser one as minor axis and "θ" as the desired angle of derotation. The value of arc length will be thus obtained. The segments of the etched line are now rotated along the obtained arc length by measuring with a flexible ruler. The osteotomy is fixed with the desired implant. Postoperative computed tomographic scan may be performed to measure and confirm rotational correction (Table 1).

CALCULATION OF ARC LENGTH

Let a be the length of the semi major axis (ie, half width of measured mediolateral width), b the length of the semi minor axis (half width of anteroposterior width), θ the desired rotational correction angle in degrees. Assuming if the rotation starts from the minor axis to the major axis, the arc length corresponding to the rotation is given by the formula

$$d = a \times E(\arctan((b/a) \times \tan(\theta)) \mid 1-(b/a)^2),$$

where E (x|m) is the elliptic integral of the second kind. Many scientific computing packages implement E (x|m) and this formula can be used to calculate the arc length easily. For example, Wolfram Alpha offers a web-based interface to do this calculation. If one inputs the following into Wolfram Alpha website: www.wolframalpha.com

$$15 \times \text{Elliptic } E[\text{Arctan}[12.5/15 \times \text{Tan}[40 \text{ degrees}]],\ 1-(12.5/15)^2].$$

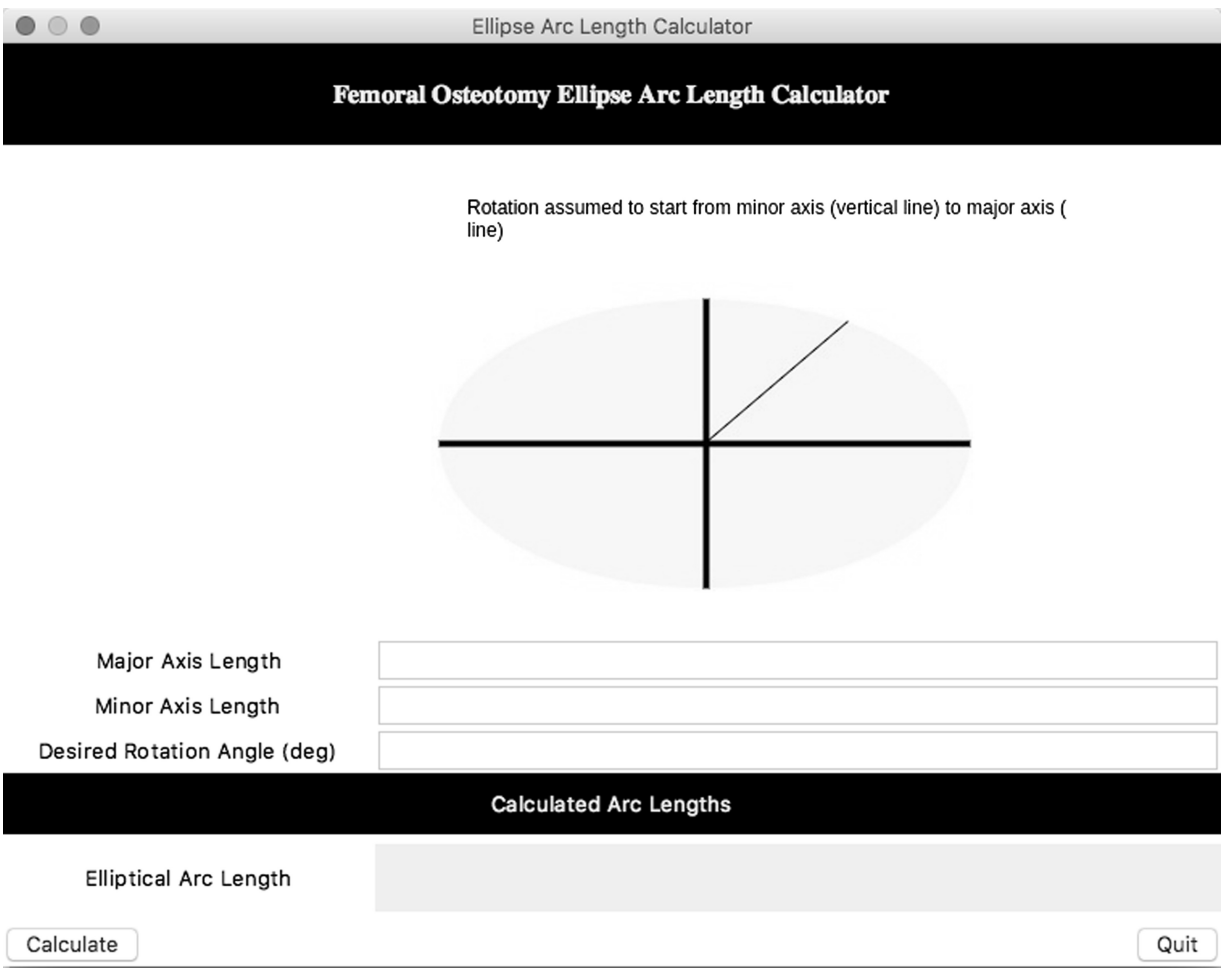

FIGURE 2. Screenshot of the html application showing the variables and output.

Here we have chosen $a = 15$ mm, $b = 12.5$ mm, $\theta = 40$ degrees. The result is computed immediately. In this case, the output is 8.99 mm.

However, expecting clinicians to enter complicated notation like above is not feasible and we have chosen to provide a simplified interface to do the computation. We have implemented a software application to carry out the computation. The software is available both as a desktop python application and a standalone html page.

We have implemented a program that takes as input the length of the major axis, the length of the minor axis and the desired rotation angle in degrees (presuming that the rotation starts from the minor axis to the major axis—laterally or medially). The program calculates the following integral numerically to arrive at the elliptical arc length:

$$\text{sqrt}(((\text{min\_ax}/2)^2)\times\sin(x)^2+((\text{maj\_ax}/2)^2)\times\cos(x)^2).$$

The lower limit of integration is 0 and the upper limit is:

$$\arctan\left(\left(\text{min\_ax}/\text{maj\_ax}\right)\times\tan(\text{rot\_angle})\right),$$

where, maj_ax is the entire length of major axis; min_ax, the entire length of minor axis, rot_angle, the desired rotation angle (converted by program from degrees to radians) (Figure 2).

DISCUSSION

Cobeljic et al[3] have described a similar technique in determining rotational correction osteotomy in children with cerebral palsy. It uses a set of tables wherein the calculated femoral measurements are plotted during surgery. They have mentioned about the drawback of their study in having considered the cross-sectional shape of proximal femur to be circular rather than elliptical. They have calculated the shortest length between the displaced segments, that is, chord length, instead of arc length which is another approximation. Our formula works for any bone whose cross section resembles a circle or ellipse. Hence, its applicable to any age group and multiple sites of a long bone. We have calculated the arc length instead of chord length which makes the correction more accurate.

Another popular technique of rotational deformity correction is using K wires. K wire is inserted into the bone, proximal, and distal to the osteotomy at the desired correctional angle to each other, using an angle guide. Following osteotomy, the fragments are rotated such that the wires are aligned parallel to each other and later fixed with an implant. The limitation of this technique lies in directing the K wires exactly to the center of the femur, which is the anatomic CORA of the rotational deformity. This is technically demanding. In addition, the K wires sometimes pose a hindrance in reduction of the fragments or use of plate holding forceps.

The provision of software to assess rotational correction makes intraoperative calculation less cumbersome and use of K wires can be avoided. Moreover, the geometrical accuracy of in our technique, unlike previous studies will yield better results and thus averts the possibility of a second correction surgery.

The limitation of our study is that the shape of femur is approximated to the closest geometrical shape, that is a circle or ellipse. Measurement error is possible, which is common with all the other techniques.

CONCLUSIONS

Our study provides the closest possible geometric approximation in calculating the magnitude of rotational deformity correction of any long bone, the cross section of which resembles a circle or an ellipse. Further studies are required to validate its accuracy, feasibility, and reproducibility for clinical use.

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Fibular Nail/Strut Graft for Hindfoot Fusion

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Summary: Tibiotalocalcaneal arthrodesis is a salvage procedure for end state pathologies of the hindfoot. Cases of primary failure can be a management challenge especially in failed intramedullary nail fixation. Inlay fibula strut grafting can be useful in such settings; however, many surgeons consider it a challenging approach. We describe our simplified approach for achieving successful fibula inlay strut grafting for hindfoot fusion. Using this approach, we achieved radiographic union in 81% (13/16) of hindfoot fusion revisions.

Key Words: failed tibiotalocalcaneal arthrodesis—inlay—strut graft—Charcot arthropathy—nonunion.

(*Tech Orthop* 2018;33: 125–127)

Tibiotalocalcaneal arthrodesis (TTCA) is a salvage procedure in cases of concomitant severe pathology of the tibiotalar and subtalar joints. Common indications include talar avascular necrosis, failed total ankle arthroplasty, and several severe autoimmune and inflammatory arthropathies. Surgical success is usually achieved in about 80% to 90% of cases, leaving 10% to 20% of cases in need of further management strategies. Some of these remedial strategies include the use of iliac crest bone graft and bone stimulation.[1] One less commonly explored management strategy for failed TTCA is the use of a fibular strut graft. Fibular strut grafting was first described by Lexer in 1906.[2] The purpose of this paper is to discuss the technique and advantage of the fibular strut graft as an effective salvage in cases of TTCA in high-risk patients and failed primary surgery.

SURGICAL TECHNIQUE

Lateral Exposure and Fibula Harvesting

The patient is positioned supine on the fluoroscopy table with a well-padded tourniquet on the upper thigh. A sandbag is placed under the ipsilateral hip to enhance the visibility of the lateral side of the foot and ankle. A 10 cm curvilinear incision is made over the distal 6 to 8 cm of the fibula, extending inferiorly and anteriorly over the sinus tarsi toward the base of the fourth metatarsal. This creates an inter-nervous plane between the superficial peroneal nerve anteriorly and the sural nerve posteriorly. Full-thickness skin flaps are developed along the skeletal plane. The periosteum is stripped from the fibula anteriorly and posteriorly, and the incision is carried on distally to expose the posterior facet of the subtalar joint and the sinus tarsi. A sagittal saw is then used to create a beveled cut at a 45-degree oblique angle using the desired length of fibula (see Video, Supplemental Digital Content 1, http://links.lww.com/TIO/A6, Video showing harvesting and preparation of fibular graft). The author recommends this cut be about 6 to 8 cm above the talocrural joint. In addition, use of a burr to contour the fibular edges may be undertaken for more smoothness and ease of insertion. The obtained fibular strut is then decorticated, drilled, and its distal end stripped of its cartilage (see Fig. 1, sample fibular strut graft after harvesting, cortical stripping, and drilling). This decortication step is essential to allow invasion of new bone onto the graft for incorporation. Through the same incision, the tibiotalar and subtalar joint are thoroughly prepared in the standard manner. On completion of joint preparation, the foot is placed in neutral ankle position in the sagittal plane, 5 degrees of external rotation in relationship to the tibial crest and 5 degrees of hindfoot valgus while maintaining a plantigrade foot. Temporary fixation using Kirschner wires (K-wire) may be used to achieve appropriate positioning. K-wire positioning must take into account, the later step of reaming and strut graft placement.

Plantar Exposure and Fibular Graft Placement

A guide pin is placed 1 to 2 cm distal from the subcalcaneal fat pad to locate the starting point for fibula nail insertion (if not performed previously). This starting point should be determined using lateral fluoroscopic guidance. Lateral, anterioposterior, and axial views are used to confirm placement after insertion. With satisfactory positioning, a 3 to 4 cm longitudinal incision is made in the starting point on the plantar aspect of the heel pad. Blunt dissection is developed down to the plantar fascia, which is split longitudinally, and then down to the plantar os calcis. A guide wire is inserted through the plantar incision into the calcaneus to pierce the

FIGURE 1. Sample fibular strut graft after harvesting, cortical stripping, and drilling. full color online

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The authors declare that they have nothing to disclose.

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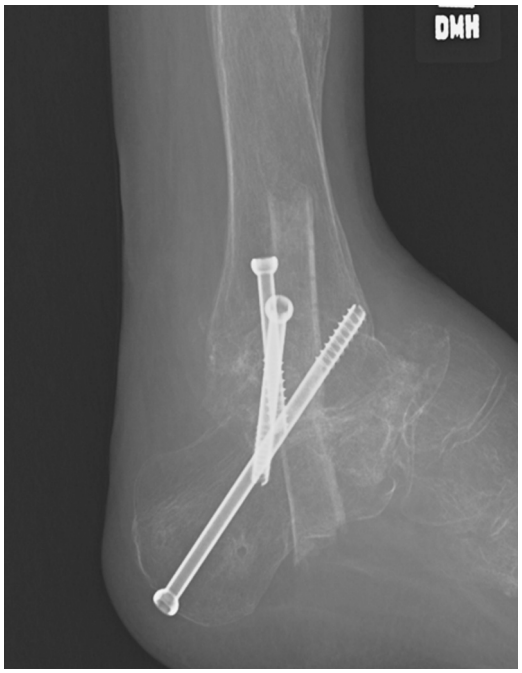

FIGURE 2. Postoperative radiograph for a Charcot Marie patient managed by fibular strut graft and ring fixator (removed). Note that the patient had asymptomatic talonavicular arthritis.

center of the talus and pass 3 or 4 inches up the center of the medullary cavity of the tibia. A series of flexible reamers are used to open the tibiotalocalcaneal canal, reaming to a diameter of 1 to 2 mm larger than the outer diameter of the fibular strut (see Video, Supplemental Digital Content 2, http://links.lww.com/TIO/A7, Video showing insertion of guide pin and reaming for fibular graft). Appropriate foot alignment must be maintained during the reaming step. The fibular graft is then loaded over the guide wire and advanced to flush with the calcaneus using a universal TTC nail extractor (in our case) or a bone tamp/impactor. This should fit the intramedullary (IM) space like a slightly oversized square peg. A few mallet taps may be used to ensure close coaptation and compression of the graft in the IM space (see Video, Supplemental Digital Content 3, http://links.lww.com/TIO/A8, Video showing insertion of the fibular strut graft). Joint immobilization is then achieved using 6.5-mm cancellous screws. The senior author recommends use of at least 2 screws to achieve optimal fixation while avoiding screw contact with the fibular strut graft in order to prevent graft fracture.

RESULTS AND DISCUSSION

Transarticular fibular inlay strut grafting/fibula nail has 3 major advantages: (1) it is an autograft with osteogenic, osteoinductive, and osteoconductive properties; (2) it carries limited morbidity especially because the lateral surgical approach serves to harvest the graft and prepare the joints in the classic manner; and (3) the fibular graft provides mechanical fixation (strut effect) that mimics an IM rod. Although autogenous iliac crest bone graft remains the gold standard and most widely used grafting technique, the reported high rate of complications such as postoperative hematoma, persistent numbness, superficial/deep infections, and chronic pain associated with harvesting the graft can be avoided. The

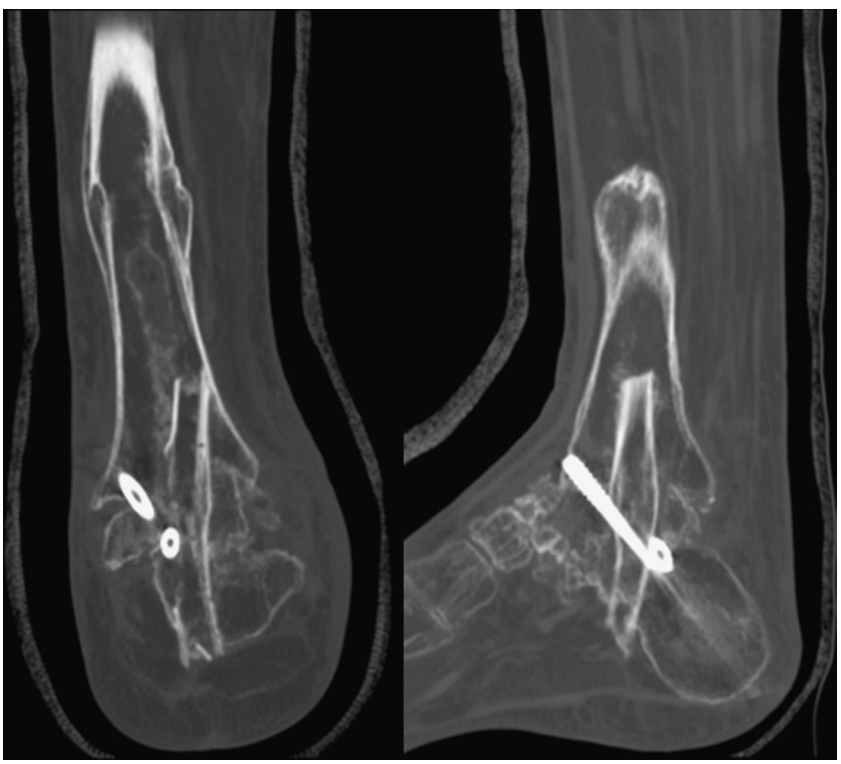

FIGURE 3. Anterioposterior (left) and lateral (right) computed tomography of the same patient at 5 months postoperatively showing incorporation of the fibular strut graft with the tibia, talus, and calcaneus.

transarticular-free fibular strut graft presents an attractive alternative means to autografting in failed TTCA or in cases of high concern for fusion failure. In particular, atrophic nonunions are one major indication for the fibular strut technique. The use of the technique is especially important for failed IM TTCA in which, the IM space would otherwise be left void. Monaco et al[1] reported 2 successful cases of fibular inlay strut grafting following IM nail infection. In another study of patients with posttraumatic arthritis and severe osteopenia, Ebraheim et al[3] reported successful use of the IM fibular strut graft technique for TTCA. All 4 patients in that study achieved fusion with no complications reported.

Different techniques other than bone grafting have been described to reduce the nonunion risk when performing TTC arthrodesis particularly in high-risk patients such as those with Charcot arthropathy and diabetes. Some of these techniques include bone stimulation and use of bone morphogenic proteins (BMPs). Bone stimulators have been used in primary and revision hindfoot surgery with Donley and Ward[4] reporting a 92% union rate for ankle and hindfoot fusions. Similarly, Bibbo et al[5] reported an overall fusion rate of 96% in 112 fusions that received BMPs adjunctively. However, reported associations of BMPs and carcinogenesis deter their widespread use.[6] Of note, these adjuvant strategies for high-risk TTCA or failed TTCA are very costly and inaccessible to the average patient.

In our experience, we used the fibular inlay strut graft technique for cases of nonunion, talar avascular necrosis, Charcot deformity, paralytic conditions, rheumatoid arthropathy, infection such as osteomyelitis, and as an exchange nail for failed TTC fusions. In these cases, 81% (13/16) of patients (10 males, 6 females; mean age = 54 y; mean BMI = 30.4 kg/m^2) went on to achieve union as confirmed by computed tomographic scan (see Figs. 2, 3, showing postoperative radiograph and computed tomographic scan in 1 patient). Six patients developed wound dehiscence that was successfully managed by repeat surgical closure (2) or advanced wound care (4). One patient developed intraoperative fracture of the fibular graft (but still achieved union). Of importance, the patient population we targeted for these surgeries were high morbidity patients with such comorbidities as chronic osteomyelitis, Charcot arthropathy with poorly controlled diabetes, and immunocompromised status. This high morbidity is likely responsible for the significant occurrence of wound dehiscence that we encountered. A detailed report of our experience is yet to be published.

Despite the technical difficulties associated with proper fitting of the fibular strut to the reamed IM space as well as the inferior vascularization of the fibular strut (being an avascular autograft), our experience with the fibular strut technique was favorable overall. This technique should be highly considered in cases of failed IM fixation TTCA or cases with high risk for nonunion.

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Comparison of Continuous Adductor Canal Catheters and Single-shot Peripheral Nerve Blocks Providing Analgesia After Unicondylar Knee Replacement, as Part of an Enhanced Recovery After Surgery Program

Jonathan A. Paul, DO and Meg A. Rosenblatt, MD

Summary: With the current trend toward ambulatory joint replacements, it is important to identify the approach to postoperative analgesia which best balances comfort and mobility. Adductor canal blocks provide analgesia after unicondylar knee replacement and can be performed with either an infusion catheter [adductor canal block catheter (ACB-C)] or as a single-shot injection [adductor canal block single-shot injection (ACB-SS)]. We conducted a retrospective analysis comparing the perceived quality of analgesia achieved by the 2 techniques, hypothesizing that patients receiving ACB-Cs would have less opioid consumption and lower pain scores than those who received ACB-SSs. After Institutional Review Board approval, we identified patients who underwent unicondylar knee arthroplasty between August and December 2015. Patients designated American Society of Anesthesiologists physical status 1 to 3 were included. Those discharged home on postoperative day (POD) 0 or provided an alternative nerve block were excluded. The primary outcome was opioid consumption over POD 1. Morning and afternoon pain scores were also evaluated. Of the 125 patients identified, there were 17 exclusions. Of those remaining, 69 received an ACB-C and 38 received an ACB-SS. The median amount of opioid use was lower in the ACB-C group than in the ACB-SS group [12 mg (8, 16) vs. 26 mg (20, 31.5), $P < 0.0001$]. Patients treated with ACB-Cs had lower pain scores in the morning [0 (0, 1) vs. 3.5 (0, 5), $P < 0.0001$] and afternoon [0 (0, 0) vs. 4 (0, 5), $P < 0.0001$] on POD 1. Our data suggest an association between adductor canal catheters and both lower opioid consumption and pain scores. A prospective randomized trial is required to confirm this finding and help determine the optimal intervention.

Key Words: unicondylar knee replacement—regional anesthesia—adductor canal peripheral nerve blockade—ambulatory joint replacement.

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There is an increasing interest in the use of unicondylar, as opposed to total knee replacements for patients with single compartmental degenerative disease of the knee. Although there is controversy about the incidence of higher revision rates, the unicondylar approach allows a smaller incision, less blood loss, faster recovery, and patients are more likely to be candidates for ambulatory surgery.[1] As efforts are made to refine enhanced recovery after surgery (ERAS) pathways for this procedure, and promote the ability to be performed on an ambulatory basis, there is a need to determine the optimal regional anesthesia technique that balances pain control, mobility, and safety.

Adductor canal blocks are replacing femoral nerve blocks as the preferred approach to analgesia after knee replacement. The branches of the saphenous and obturator nerves in the more distal adductor canal are primarily sensory. As a result, the functions of sartorius and quadriceps muscle groups tend to be spared with adductor canal blocks, although 1 study reported vastus medialis weakness in 8% of patients.[2] This motor sparing should decrease the risk of patient falls and facilitate early postoperative mobilization with physical therapy. Superior quadriceps muscle strength, noninferiority in analgesia and opioid intake, and decreased time to mobilization (but not to discharge) have all been described.[3–5] After incorporating adductor canal blocks into an ERAS program, 1 major institution found a reduction in length of stay after total knee replacement.[6]

Adductor canal blocks can be performed with placement of a continuous infusion catheter [adductor canal block catheter (ACB-C)] or single-shot injection [adductor canal block single-shot injection (ACB-SS)]. As compared with placebo, there is evidence that ACB-C use reduces postoperative opioid consumption.[7] A recent study provides the only early assessment of the relative efficacy of these 2 approaches in the setting of total knee replacement.[8] The findings suggest that superior analgesia is achieved with an ACB-C as compared with an ACB-SS. The use of these techniques specifically for unicondylar knee arthroplasty has yet to be studied. Both ACB-Cs and ACB-SSs are used to provide analgesia after this procedure at our institution and there is equipoise regarding which is better for pain control, mobility, and discharge readiness. The most important determinant of superiority may be analgesic efficacy, as patient mobility and satisfaction correlate inversely with reported pain scores.[9] We performed a retrospective analysis to compare the perceived quality of pain control achieved by the 2 techniques in patients specifically undergoing unicondylar knee replacement. Our hypothesis was that patients receiving ACB-Cs would have decreased opioid consumption and lower pain scores on the first postoperative day (POD) as compared with those who received ACB-SSs.

METHODS

After receiving Institutional Review Board approval, we identified patients who underwent unicondylar knee arthroplasty between August and December 2015, with either of 2 primary surgeons (one who prefers ACB-Cs and the other ACB-SSs). Criteria for inclusion consisted of being American Society of

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Anesthesiologists (ASA) physical status 1 to 3 and having received either an ACB-C or ACB-SS for postoperative analgesia. Those patients discharged home on POD 0 or who were provided an alternative nerve block were excluded.

The hospital's electronic medical record (Prism, GE Healthcare, UK) and the anesthesia case database (CompuRecord, Philips, MA) were reviewed to gather data for patients meeting inclusionary requirements. The primary outcome was total postoperative opioid consumption over 24 hours. Quantities of all opioids administered were converted to equivalents in milligrams of intravenous morphine, according to American Pain Society guidelines and relevant review articles.[10–12] Pain scores following an 11-point (0 to 10) numeric rating scale were evaluated as a secondary outcome. The highest numeric rating scale scores during the morning (06:00 to 10:00) and afternoon (12:00 to 16:00) on POD 1 were recorded, to ensure adequate time for patients to have been seen by physical therapy teams.

Patients undergoing joint replacement at our hospital follow a standardized ERAS clinical pathway, unless individual elements are contraindicated. Preoperatively, patients receive oral acetaminophen 975 mg, pregabalin 75 to 150 mg, and celecoxib 400 mg. Intraoperatively, patients receive a spinal anesthetic and an intra-articular injection, administered by the surgeon, with preservative-free morphine 5 mg, ropivacaine 300 mg, and ketorolac, 30 mg diluted to 100 mL with preservative-free saline. Either an ultrasound-guided ACB-C or ACB-SS is administered on arrival to the postanesthesia care unit under direct supervision of an experienced attending anesthesiologist. Both regional techniques involve a bolus of 0.2% ropivacaine or 0.25% bupivacaine and patients receiving catheters use patient controlled anesthesia with continuous infusions of 0.1% bupivacaine 5 mL/h with a 5 mL bolus and lockout of 60 minutes. The acute pain management service follows all those with nerve block catheters. A supplemental, multimodal analgesic regimen is prescribed by the orthopedic team postoperatively and includes oral narcotics on a pro re nata basis.

Normally distributed, parametric data were analyzed using the Student *t* test. Ordinal demographic data were evaluated with the Pearson χ^2 test or Fischer exact test. Nonparametric outcome data were analyzed using the Mann-Whitney *U* test.

RESULTS

A total of 125 patients underwent unicondylar knee replacements with the 2 surgeons included in this study. Seventeen were excluded because of discharge home on POD 0 and each of these patients received an ACB-SS. One patient was excluded for having received a femoral nerve block. Of those remaining, 69 patients received an ACB-C and 38, an ACB-SS. The groups were not significantly different with respect to age, body mass index, side of procedure, ratio of men and women, or proportion of those receiving bupivacaine versus ropivacaine as an initial bolus drug (Table 1). However, there were a larger proportion of ASA 3 patients in the ACB-SS group.

The median amount of opioid use in the first 24 hours postoperatively was lower in the ACB-C group than in the ACB-SS group [12 mg (8, 16) vs. 26 mg (20, 31.5), respectively, $P < 0.0001$]. Patients who received ACB-Cs had lower pain scores in the morning [0 (0, 1) vs. 3.5 (0, 5), $P < 0.0001$] and afternoon [0 (0, 0) vs. 4 (0, 5), $P < 0.0001$] on POD 1 (Table 2).

TABLE 1. Patient Characteristics

	All Patients (n = 107)	ACB-C (n = 69)	ACB-SS (n = 38)	*P*
Age	66 (60, 71)	66 (60, 72)	66.5 (59.5, 71)	0.78*
Sex (M/F)	29/78	16/53	13/25	0.22†
BMI	30 (27, 36)	30 (27, 35)	32 (27, 37.75)	0.37*
ASA physical status				0.003‡
I	3 (3%)	3 (4%)	0	
II	73 (68%)	53 (77%)	20 (53%)	
III	31 (29%)	13 (19%)	18 (47%)	
Operative side (R/L)	57/50	33/36	24/14	0.13†
Initial bolus drug (0.25% bupivacaine/0.2% ropivacaine)	14/93	6/63	8/30	0.19†

Quantitative data are expressed as median (25th, 75th percentile). Qualitative data are expressed as a ratio or with percentages in brackets.

*Two-sample *t* test with unequal variances.

†Two-sided Pearson χ^2 test.

‡Fisher exact test.

ACB-C indicates adductor canal block catheter group; ACB-SS, adductor canal block single-shot injection group; ASA, American Society of Anesthesiologists; BMI, body mass index; F, female; L, left; M, male; R, right.

DISCUSSION

Our data suggest an association with adductor canal catheters and lower opioid consumption and pain scores in patients undergoing unicondylar knee replacements. It could be argued an advantage of a single-shot injection is improved mobility from not being tethered to a pump, which may make a surgeon more likely to discharge the patient on the day of the procedure. However, these patients would likely have suboptimal analgesia at home and be at risk for readmission to the hospital to manage pain. Furthermore, safety has been established in appropriate patient populations with at-home femoral nerve catheters.[13] Adductor canal catheters, therefore, should not be barriers to an ambulatory pathway. In a survey of those with continuous interscalene catheters after outpatient shoulder surgery, most patients reported less awakening from sleep and no difficulty in removing catheters independently or with family member or caregiver assistance.[14] A retrospective analysis of patients discharged with continuous interscalene, popliteal, and femoral catheters revealed that only 2 of 620 subjects had complications, which were temporary and resolved within 6 weeks of surgery.[15]

Limitations to our investigation include a baseline difference in ASA scores in the single-shot group and variation in operative technique between surgeons. All patients discharged home on the day of surgery were in the ACB-SS group. We did not

TABLE 2. Postoperative Opioid Consumption and Pain Scores

	ACB-C	ACB-SS	*P*
IV morphine (mg), first 24 h postoperatively	12 (8, 16)	26 (20, 31.5)	< 0.0001
POD 1 morning pain score	0 (0, 1)	3.5 (0, 5)	< 0.0001
POD 1 afternoon pain score	0 (0, 0)	4 (0, 5)	< 0.0001

Data expressed as median (interquartile range). All comparisons made with 2-sided Mann-Whitney *U* test.

ACB-C indicates adductor canal block catheter group; ACB-SS, adductor canal block single-shot injection group; POD 1, postoperative day 1.

examine the impact of preoperative narcotic use on postoperative outcomes nor the quality of postoperative mobility. We were also unable to attain comprehensive data regarding the duration of catheter use and supplemental bolus requirements in the ACB-C group. A prospective randomized trial is needed to address these limitations. As we refine our techniques to support ERAS efforts and build an ambulatory clinical pathway, it is increasingly important to establish the relative efficacy of regional techniques for unicondylar arthroplasty.

ACKNOWLEDGMENT

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