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NARRATIVE REVIEW

Blood flow restricted training: applications, mechanisms, and future directions

Bretton Thurston[1] and Jamie F. Burr[1]

Abstract

There is a growing body of research suggesting that low intensity resistance training, completed under reduced blood flow by external compressive force on the vasculature, can elicit adaptations similar to traditional resistance training, but at a significantly reduced exercise intensity. Blood flow restriction (BFR) training was developed as a method of maintaining skeletal muscle mass in the ageing population, but advances in this area of research have broadened its application for use in both performance and rehabilitative populations. There are several proposed mechanistic theories; however, a definitive explanation is still unclear. The purpose of this narrative review is to discuss the use of blood flow restriction in performance and rehabilitative applications, examine potential mechanisms of action, and review areas of limitation within research practices. This article also examines BFR training during transient involuntary muscle contractions evoked by transcutaneous electrical muscle stimulation as a novel training intervention for individuals with reduced motor capability. BFR is an attractive training method that could be considered as an effective modality for use by appropriately trained health and fitness practitioners, especially those working with individuals that require modified resistance training programming. **Health & Fitness Journal of Canada 2017;10(1):3-16.**

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From [1] Human Performance and Health Research Lab, University of Guelph, 50 Stone Road East, Guelph, Ontario. Email: burrj@uoguelph.ca

Introduction

Skeletal muscle mass is one of the largest sites of cellular energy metabolism in the human body and is fundamental for the support of bone structure and control of blood glucose through insulin and contraction stimulated glucose uptake. In the general population, reduced skeletal muscle mass is caused by inactivity and can lead to attenuated exercise capacity, muscle size and reduced sensitivity to plasma insulin (Loenneke et al., 2012a; Andersen et al., 2003). Diminished skeletal muscle mass can also be caused by injury or neurological diseases, which can lead to reduced motor control. As such, the significance of maintaining physical activity in some capacity is important in all populations.

Reference to widely accepted physical activity guidelines for resistance training suggest that ~70% of 1 maximal repetition (1RM) or more is required to produce hypertrophic adaptations and exercising at <60% of 1RM fails to recruit all fibre types (Schoenfeld, 2013). Fibre recruitment is characterized by the size principle, which indicates that at low intensity, oxidative myosin heavy chain (MHC) type I muscle fibres are recruited, and as intensity increases, larger MHC type IIa oxidative and type IIx glycolytic fibres are subsequently recruited. Resistance training produces muscular adaptations as a consequence of metabolic stress, which is attributed to increased hormonal secretion of growth hormones (Reeves et al., 2005), the generation of reactive oxygen species, hypoxia and muscle fibre cell swelling (Loenneke et al., 2012c) resulting in increased Akt-mTOR pathway signalling and protein synthesis (Loenneke et al., 2009).

A way in which there is potential to gain the same skeletal muscle benefits of resistance training without the need to complete higher intensity resistance exercise is through the technique of blood flow restriction (BFR). Blood flow restriction training involves temporary occlusion of a limb combined with low intensity exercise. There is a growing body of research suggesting that low intensity resistance training, completed while temporarily reducing blood flow using an external compressive force on the vasculature, can elicit adaptations similar to traditional resistance training, but at a significantly reduced exercise intensity. The application of BFR during resistance training at intensities as low as 20% 1RM have been shown to be as effective as resistance training at ~70% 1RM (Loenneke et al., 2012a; Loenneke et al., 2011b; Slysz et al., 2016; Scott et al., 2014). This technique is therefore valuable in populations where high intensity resistance training is not possible. Currently, this technique is applied to a limb with the goal of producing venous pooling, which is an important aspect of reducing the threshold for stimulus; however, earlier research utilized a complete suprasystolic occlusion method (Cook et al., 2007; Fujita et al., 2007; Takarada et al., 2000; Sato et al., 2005b, Takano et al., 2005) until it was determined that lower cuff pressures, which only produce venous pooling, may be safer and have similar efficacy.

Applications of use

BFR was originally developed by a Japanese researcher, Yoshiaki Sato, as a solution to help prolong physical independence in the ageing population, but has now grown to have a wide range of applications. Yoshiaki Sato popularized BFR training through the development of the KAATSU device, created during the 1970's (Sato, 2005a). Sato recognized that a large percentage of the Japanese population would soon be elderly and an alternative method to strength training, with less strain on the joints, was necessary. The KAATSU allowed for a simple and non-invasive method of strength training at a reduced load that still maintained the benefits associated with resistance training intensities equivalent to ~70% 1RM exercise (Sato, 2005a).

More recently, BFR has been tested in clinical case studies, which have suggested its use in rehabilitation for procedures such as reconstructive knee surgery (Ohta et al., 2003; Lejkowski and Pajaczkowski, 2011), while other researchers have utilized BFR for training and performance benefits (Yasuda et al., 2005; Abe et al., 2005a; Abe et al., 2006; Yasuda et al., 2006; Abe et al., 2009; Karabulut et al., 2010; Abe et al., 2010a). Training adaptations with BFR have been examined using various modes of exercise and have produced similar effects on strength and hypertrophy. The effectiveness of BFR training using a wide range of exercise modes allows BFR to be an attractive intervention strategy for therapists prescribing rehabilitation plans that can be tailored to an individual and their sport or lifestyle specific needs. For example, applying BFR while exercising on a stationary bicycle can promote otherwise unexpected hypertrophic adaptations (Loenneke et al, 2011b; Abe et al., 2010a), while removing the need for increased balance and coordination associated with dynamic strength exercises. Literature shows improved muscular hypertrophy and strength performance (Loenneke, 2011b) using both dynamic resistance training exercises and endurance style exercises (i.e. treadmill, cycling) with the application of BFR. Both intermittent and continuous exercise methods have demonstrated similar improvements in hypertrophy (Abe et al., 2006; Abe et al., 2010a; Beekley et al., 2005); however, there is yet to be a standardized protocol using BFR for either. This lack of standardization causes challenges in quantifying which method of exercise is superior as training duration, frequency, and occlusion pressure can all impact apparent results and pose as potential limitations. BFR during continuous endurance exercise has been examined in several studies (Abe et al., 2006; Abe et al., 2009; Abe et al., 2010a; Beekley et al., 2005; Ozaki et al., 2011). When using BFR during treadmill walking, researchers have employed walking protocols using speeds of ~50 meters/min for multiple short bouts (~2 minutes) (Abe et al., 2006) and, also at higher intensities, upwards of ~67 meters/min for 20 minutes of exercise (Abe et al., 2010b). In essence, BFR can be used to navigate barriers such as balance or motor control that may limit one's resistance training abilities, while providing little in terms of elevated risk (Loenneke, 2011c).

Blood Flow Restriction - performance

Regardless of chosen sport discipline, most athletes rely on resistance training as a direct, or supplemental, measure to improve sport performance in some capacity. Athletes may use resistance training to build size and strength for injury prevention and improved on-field performance or for increasing muscle mass, leading to improved power generation and faster race times. When competition schedules include long in-season training phases, very little time may be left for the incorporation of off-season hypertrophy and de-loading phases within a periodized training program. Therefore, BFR training during a de-loading phase can produce a sufficient stimulus for hypertrophic adaptation, while reducing stress on joints and tendons. Lowery and colleagues (2013), examined BFR through a well-designed cross over study using two phases of periodization; four weeks of BFR using 30% 1 RM, or four weeks of high intensity resistance training. Continued development of muscle strength and hypertrophy was demonstrated regardless of training phase order (Lowery et al., 2013), providing support that BFR training can be implemented during de-loading training phases for an acute period and not mitigate the results of other training phases.

Individual training status does not appear to affect the efficacy of BFR training, as both novice and experienced exercisers can benefit from application of this technique. However, exercise volume appears to influence hypertrophy through BFR, as there appears to be the largest hypertrophic effect in groups exercising two to three sessions per week, while those exercising greater than four sessions per week seems to demonstrate attenuated improvements (Loenneke et al., 2011b). The exact mechanism for this effect remains unclear. BFR training use in athletes has been extensively studied. Takarada and colleagues examined BFR training with elite level athletes, who exhibited significant increases in knee torque and muscle cross-sectional area compared to the control group (Takarada et al., 2002). Similarly, using competitive male track and field speed/power athletes (sprinters and jumpers), Abe and colleagues examined the effect of KAATSU training applied during squat and leg extensions on sprint/jump performance (Abe et al., 2005b). Training at 20% 1RM with BFR increased leg strength by ~5% compared to the control group that completed an identical training program without BFR. Results from on-field testing indicated a significant improvement in 30m dash times, particularly during the initial acceleration phase (start to 10m) of the sprint performance. Similar results were seen in high-intensity sprint team sport athletes, who, after 5 weeks of KAATSU training, improved both maximum voluntary contraction and maximal number of repetitions performed at low intensity (20% 1RM) (Manimmanakorn et al., 2013a; Manimmanakorn et al., 2013b). While the focus of this review is specifically on BFR training, it should not be overlooked that some effects in this regard could also be associated with an ischemic preconditioning stimulus (Incognito et al., 2016), especially if a close temporal relationship between BFR and exercise performance existed.

Blood Flow Restriction- Rehabilitation

In situations where an individual is faced with a prolonged period of immobilization such as injury or illness, muscular atrophy can be of concern. Muscular atrophy is characterized as the reduction in myofibril cross sectional size caused by activation of cell degradation pathways. This occurs because maintaining muscle mass is metabolically costly and to maintain homeostasis the body atrophies areas of disuse, while providing support to areas of use through various pathways (Glass., 2005). To limit muscular degradation, BFR can be implemented shortly after an individual has regained sufficient mobility to safely rebuild muscle while putting reduced strain on joints and tendons until they have regained the strength required for traditional resistance training loading (Ohta et al., 2003). Blood flow restriction training has demonstrated to be particularly beneficial for rehabilitation of anterior cruciate ligament (ACL) injuries (Ohta., 2003). A study examining training during the first 16 weeks following ACL surgery, had participants divided into 2 groups that participated in either traditional ACL rehabilitative exercise training with BFR or a control group that completed the same exercises without any occlusion. After 16 weeks, the BFR group had significantly improved extensor strength compared to the non-occluded group. Muscle cross sectional size was also significantly increased compared to the control following the training period. Recovery from ACL surgery typically takes 4-6 months, during which significant muscular atrophy can occur, therefore, intervention strategies to reduce this time frame are beneficial.

Interestingly, research has suggested that introducing BFR before regaining mobility, without any type of exercise training, can also help to prevent muscular atrophy; however, research in this area is relatively limited (Takarada et al., 2000; Kubota et al., 2008). It is theorized that the prevention of muscular atrophy through the application of BFR is partially due to cell swelling, which results from blood pooling, metabolite accumulation and reactive hyperaemia, which signals an increase in mTOR activity (see mechanisms).

The benefits of BFR training may not be limited to locally activated muscles (Madarame et al., 2008). Resistance training has demonstrated to produce cross-transfer effect, wherein training of a single limb, not only increases muscular strength and hypertrophy in the trained limb, but also promotes similar adaptation in the contralateral, untrained limb. Research suggests application of BFR on a single limb can produce a similar systemic effect and augment hypertrophy in remote muscles during subsequent bouts of resistance exercise within the same session (Madarame et al., 2008; Slysz & Burr, 2017). This phenomenon of strength cross-transfer between limbs is thought to be due to neurological adaptation, increased circulating testosterone and growth hormones (Madarame et al., 2008); however, there is conflicting evidence indicating increased growth hormone (GH) may not be responsible for hypertrophic adaptations (Morton et al., 2016). Although still understudied, cross-transfer effects could be a beneficial stimulus during immobilization to prevent atrophy. It is possible that applying BFR to an immobilized limb without an exercise stimulus and using BFR on the contralateral limb while exercising could further promote hypertrophy; however, whether or not these effects are additive is yet to be investigated.

Between Study Variations: Factors influencing BFR efficacy

The literature suggests there are numerous factors associated with BFR, which can influence its efficacy. Factors including cuff dimensions, cuff material, inflation pressure and exercise mode have been suggested to influence BFR effectiveness in producing strength and hypertrophic adaptation. Currently, there are a few popular devices for BFR training, which employ differing cuff dimensions that may influence outcomes. The KAATSU device is commonly employed by research teams using a 5 cm wide cuff, which is the narrowest popular BFR device (Sato, 2005a; Yasuda et al., 2005; Abe et al., 2005a; Abe et al., 2006; Yasuda et al., 2006; Abe et al., 2009; Karabulut et al., 2010; Abe et al., 2010a; Takarada et al., 2013; Cook et al., 2007; Fujita et al., 2007; Fahs et al., 2011; Rossow et al., 2011). Traditional automated or manual blood pressure cuffs are also commonly used in research, with cuffs measuring ~12 cm to 18.5 cm wide (Burgomaster et al., 2003; Gorgey et al., 2016; Takada et al., 2012; Teramoto et al., 2006); however, the popularity of manual blood pressure cuffs for BFR training is far less than the KAATSU device, or other automated tourniquet systems. A number of studies have utilized elastic knee wraps for BFR (Loenneke et al., 2010; Loenneke et al., 2012b), which can be an attractive occlusion method because of low cost; however, research with this method of blood flow restriction appears to be less prevalent, perhaps due to underlying challenges with maintaining consistent pressure across sessions, exercises and participants.

At present, there is a wide range of cuff pressures used for BFR within the literature. Common practice for BFR pressure regularly sets occlusion at either 1.3x systolic blood pressure (SBP) or a standard suprasystolic pressure above 200 mmHg (Loenneke, 2011). Recently, sub-systolic occlusion pressures have gained popularity in the literature. Sub-systolic occlusion allows for arterial inflow and venous outflow pooling, which has been suggested to be safer for research participants, and similarly effective (Cook et al., 2007; Inagaki et al., 2011; Natsume et al., 2015) due to the relationship of relative cuff pressure to the flow of blood being non-linear (Mouser et al., 2017).

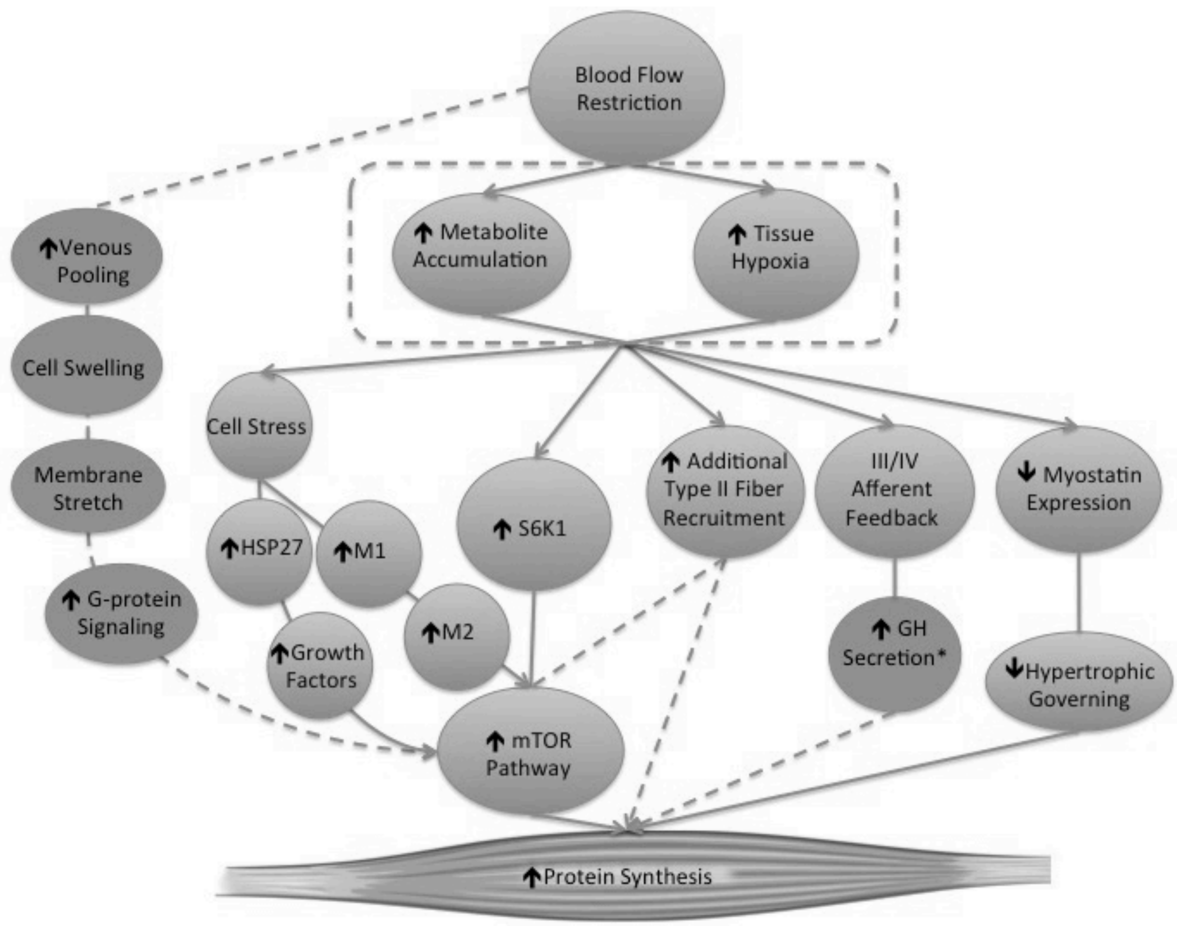
Investigations using a standardized, rigid occlusion pressure, face challenges with inter-subject differences such as leg girth or blood pressure, impacting the magnitude of BFR. Loenneke et al. suggest that occlusion at pressures upwards of 200 mmHg can become a safety concern as the pressure applied to a 5 cm wide cuff differs in absolute arterial occlusion pressure, compared to the same pressure using a 12 cm wide blood pressure cuff (Loenneke et al., 2013). This is predicted on the understanding that the level of occlusion is relative to the amount of tissue surrounding the blood vessels and the type of tissue being compressed (i.e. larger limbs require higher pressure for greater occlusion). In support of this, it has been previously demonstrated that a wider cuff will occlude arterial blood flow at a much lower pressure compared to a narrow cuff (Loenneke et al., 2011; Crenshaw et al., 1988). This is an important aspect of BFR safety as too high an occlusion pressure could, at least theoretically, cause tissue or nerve damage in certain individuals. Accordingly, the method of occlusion should be taken into consideration not only because of potential variation of results, but also due to potential safety issues for some individuals.

Dedicated BFR devices, such as the KAATSU, are made from a fabric with elastic properties that house a pneumatic bag inside the restriction belt. In comparison, traditional blood pressure cuffs are designed to be an inflatable bladder that is either airtight, or a pneumatic bag housed inside a nylon coating. There is limited evidence suggesting that certain materials are more effective; however, a previous review has suggested that cuffs with internal bladders may produce deviating pressures to what the regulator is reading (under / over estimation) (O'Brian, 1996). For this reason, it is important to validate pressure readings and appropriately assess subject limb characteristics to employ a properly fitting cuff.

Potential Mechanisms of Action

The specific mechanisms behind the benefits of BFR are not yet fully elucidated; however, there is support from several contributing theories. Research has suggested the hypoxic environment produced by BFR increases plasma GH concentrations, similarly to what is shown to occur during traditional weight training (Takarada et al., 2000). Human GH is an anabolic hormone produced in the anterior pituitary gland, which promotes muscular hypertrophy as a result of reduced pH acting on metaboreceptors and group III and IV afferent fibres (Loenneke et al., 2009). Recently, Morton and colleagues have contradicted this theory by using a 12-week training study demonstrating increased strength and hypertrophic adaptations, with no increases in sustained circulating hormones (Morton et al., 2016). West and colleagues have also indicated support for these findings (West et al., 2009; West et al., 2010).

acting on the vasculature. High intensity resistance training promotes protein synthesis, which increases the cross sectional size of a muscle fibre. It is thought that due to reduced oxygen



There is evidence that S6K1 phosphorylation in the mTOR pathway is increased in response to occluded exercise (Fujita et al., 2007). S6K1 has been shown to play a significant role in stimulating muscle protein synthesis through altered regulation of mRNA translation acting on the Akt-mTOR pathway, therefore promoting hypertrophy (Fujita et al., 2007). This is typically accomplished with high intensity resistance training, which produces hypoxia by way of muscular compression content, progressive recruitment is altered to maintain force development even in a hypoxic state (Loenneke et al., 2009). This altered recruitment pattern trains MHC-II fibres at the observed ~20% 1RM intensities unlike traditional weight lifting.

Another potential mechanism involved in chronic BFR training is the alteration of myostatin gene expression (Laurentino et al., 2012). Myostatin is a negative regulation myokine protein produced by myocytes to inhibit cell growth and is an important protein involved in muscle remodelling. Previous studies have suggested myostatin gene expression is decreased with mechanical overloading and hypoxic training as a result of metabolite accumulation (Kawada and Ishii., 2005; Loenneke et al., 2009). Reduced myostatin expression would produce improved hypertrophic effects by way of reduced hypertrophic governing.

Recently, Nielsen and colleagues demonstrated support for another potential mechanism of BFR involving increased M1/M2 macrophage and heat shock protein 27 (HSP27) content after short-term chronic BFR training (Nielsen et al., 2017). The M1 macrophage supports inflammation shortly after muscle injury to aid in the removal of cell debris through phagocytosis. The M2 macrophage is predominant in later stages of injury, where it acts as an anti-inflammatory response by promoting muscle tissue remodelling (Nielsen et al., 2017). HSP27 acts as a mediator of cellular stress, which prevents protein denaturation and aggregation after exercise. It is postulated that increased HSP27 expression reflects significant myocellular stress occurring with BFR training. It is possible that acute changes in plasma membrane permeability occurring with BFR causes a transient increased ion flux acts to signal macrophage and heat shock protein cellular stress response, resulting in increased secretion of growth factors.

Many of the mechanisms postulated in BFR are based on the concept of reduced oxygen and the accumulation of metabolites that stimulate group III and IV afferent discharge in some capacity. The alteration in group III and IV afferent discharge is thought to cause inhibition of the alpha motor neuron supplying local MHC-I fibres, therefore resulting in increased MHC-II fibre recruitment (Loenneke et al., 2012c).

While these proposed mechanisms are valid, they do not explain the adaptations that occur when BFR is applied without an exercise stimulus (Kubota et al., 2009). In this case, there is an alternative hypothesis, of blood flow induced cell-swelling, suggesting that cell swelling inhibits catabolism as a result of protein-kinase signalling pathways and growth factor signalling as an anabolic response to membrane stretch (Schoenfeld., 2010). It is thought that cell swelling could prevent atrophy and also impact cellular metabolism to be more reliant on lipolysis and sparing of protein. There are two instances where this can occur during BFR; firstly, during occlusion in the distal portion of the limb; and secondly, during the hyperaemic response of reperfusion. It is hypothesized that the increased fluid content prompts intracellular signalling of G-proteins to activate mTOR pathways without the need of physical exercise or metabolite accumulation (Loenneke et al., 2012c). Currently, it is not possible to determine definitive mechanisms of action of the physiological response to BFR and further research needs to be conducted to better determine what pathways are acting under certain circumstances.

Future Directions: Blood flow restriction during involuntary muscular contraction

It is generally accepted that implementing BFR with some form of exercise at a reduced load produces greater hypertrophic adaptation compared to BFR without any muscular activation. For some populations, particularly individuals who lack motor ability due to challenges associated with neurological disorders and spinal cord injuries, maintaining muscle mass is challenging and reduced dexterity can pose a significant barrier to completing activities of daily living. To help accommodate these unique populations, novel training interventions such as electrical stimulation have been examined in conjunction with BFR to mimic the impact of physical activity.

Recently, BFR with electrically evoked muscular stimulation (STIM) was examined as a means to increase muscle mass in spinal cord injured individuals (Gorgey et al., 2016). This study investigated participants who had incomplete tetraplegia that underwent 6 weeks of training with either STIM or BFR+STIM. After 6 weeks of training there was a significant increase in wrist flexor and extensor cross sectional size for BFR+STIM compared to STIM alone demonstrating electrical stimulation may be an acceptable substitution when voluntary muscle contraction is not possible.

Other studies have also examined the use of BFR with STIM in subjects without spinal cord injuries demonstrating a similar augmentation of training effects when BFR is added to muscular contraction (Slysz and Burr, 2017). Similar findings to previous work investigating the hormonal response to BFR and voluntary contraction (Takarada et al., 2000) have been found in a study investigating BFR+STIM (Inagaki et al., 2011). Findings demonstrate the potential efficacy for BFR+STIM as an alternative exercise stimulus to voluntary contractions. Using healthy subjects, BFR was applied while leg extension movements were electrically evoked by muscle stimulation. Acute serum GH increased in response to BFR+STIM when venous outflow was restricted at 150 mmHg (Inagaki et al., 2011). In support of other proposed mechanistic theories, locally produced metabolites also accumulated within the stimulated muscle with BFR application.

As previously indicated, there is evidence suggesting BFR can attenuate muscular atrophy without any muscular contractions (Takarada et al., 2000; Kubota et al., 2008). Given that attenuated atrophy during muscular disuse was observed with BFR alone, another study examined STIM administration during BFR using a training model that included a detraining phase, where researchers attempted to maintain hypertrophic adaptations (Natsume et al., 2015). Participants underwent 2 weeks of twice daily isometric electrical stimulation in the control leg, and BFR and electrical stimulation in the contralateral leg followed by 2 weeks of detraining. Participants displayed increased muscle thickness with BFR+STIM, which remained elevated compared to STIM alone during the first week of detraining. Further, isometric and isokinetic strength remained elevated over the entire detraining period with the BFR+STIM condition. Perhaps the evidence in this short-term detraining model suggests the BFR+STIM could also produce other benefits associated with muscular activation (i.e. physical activity) not necessarily acting on hypertrophic adaptations.

Conclusion

The use of BFR with light intensity muscular contractions through lower intensity exercise presents an attractive intervention strategy for both therapists or coaches prescribing rehabilitation and performance programming as it can be tailored to an individual and their sport or lifestyle specific needs. Utilizing BFR while training can decrease the stress and strain on joints associated with long-term weight training and can be used as a rehabilitation method for circumstances in which immobilization and reduced limb loading are unavoidable. Recent evidence has shown that BFR can be implemented with additional electrical stimulation to produce hypertrophic adaptations in individuals with limited motor capabilities. As an emerging field of inquiry, BFR training mechanisms have yet to be fully elucidated and further research is justified in this area of health sciences. Future investigations may probe to determine the ideal volume and intensity to elicit maximal hypertrophic and strength adaptations or examine potential benefits of BFR+STIM on other metabolic health related markers.

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Authors' Qualifications

The authors' qualifications are as follows: Bretton Thurston, BSc, CEP; Jamie Burr, MSc, PhD, HFFC-CEP.

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