

Blood Flow Restricted Exercise: Physical Therapy Patient Management Using Current Evidence

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ABSTRACT

CONTENT: Blood flow restriction exercise, or BFR, has emerged in recent years as a physical therapy technique. It is used to provide an exercise stimulus to patients to restore muscular size and strength. Blood flow restriction involves the combination of exercise with the use of a device to restrict blood flow into the working limb, typically through a pressurized cuff. This monograph will provide the clinician with BFR foundational knowledge that will aid decision making, patient education, and application in the clinic. We will present current best evidence on mechanisms involved, safety, selecting pressures and loads, application via resistance and aerobic exercise, emerging techniques, and how to integrate BFR at various time points in the rehab continuum. **CASE ANALYSES:** Five cases are presented that highlight how clinicians may implement BFR in the clinical setting. Cases 1 and 2 highlights using BFR for a lower extremity injury in a geriatric and a pediatric patient with successful outcomes. Case 3 highlights the application for an upper extremity injury in the shoulder to help highlight the potential for proximal, above the cuff, improvements with BFR. Case 4 highlights the use of BFR and neuromuscular electrical stimulation to achieve an analgesic effect in a geriatric patient. Lastly, case 5 highlights programming high load training in conjunction with low-load BFR for a soft tissue injury.

Key Words: hypertrophy, low load exercise, vascular occlusion

LEARNING OBJECTIVES

Upon completion of this monograph, the course participant will be able to:

1. Understand the overall safety profile of blood flow restriction.
2. Understand the physiology behind why blood flow restriction may work.

3. Identify populations for whom to consider the use of blood flow restriction.
4. Describe how blood flow restriction may be used to combat anabolic resistance.
5. Appropriately program blood flow restriction with resistance exercise based on current evidence.
6. Appropriately program blood flow restriction with aerobic exercise based on current evidence.
7. Know how to implement blood flow restriction into current practice.
8. Understand how blood flow restriction may influence pain.

INTRODUCTION

For decades, scientists have studied the physiologic responses of human tissues subjected to periods of hypoxia. These investigations continue today because the responses are many and complicated. In fact, just this year the Nobel Prize in Physiology or Medicine (2019) was awarded to 3 scientists for their study of the genomic responses to tissue hypoxia.¹ Some of the earliest investigations date back to 1937 when Alam and Smirk detailed the exercise pressor response, and 1938 when Collens and Willensky demonstrated the effectiveness of repeated intermittent vascular occlusion to reduce pain and heal recalcitrant wounds from peripheral arterial disease.^{2,3}

Scientists in the mid-eighties began to experiment in more extreme ways via animal models, detailing the protective effects of ischemic preconditioning (IPC) against reperfusion injury to cardiac tissue, and skeletal muscle adaptation to cycling under very mild blood flow restriction (BFR).^{4,5} The nineties saw researchers begin to incorporate low load isotonic exercise combined with BFR as a means of eliciting hypertrophy and increased strength when one would not anticipate those changes.⁶ This would have very obvious clinical applications if research affirmed clinical efficacy, and the safety of the technique could be demonstrated. News of this work began to spread, and exercise physiologists began to more thoroughly examine the utility of the technique, which has fostered innumerable questions and projects.

Currently, it seems clear that reducing blood flow to a working muscle helps to amplify a task's ability to cause adaptation.^{7,8} Many methodological questions remain for practitioners to have an optimal understanding of the dose response relationship, but it is certain that BFR elicits a large amount of fatigue in a short timeframe to which skeletal muscle will adapt.⁹

In this monograph, you will learn the key components to implementing BFR in a clinical setting in a safe and meaningful way. We will cover how something as simple as pedaling a bike with BFR can enhance your patient outcomes, the detailed signaling cascade that we must manipulate in order to cause skeletal muscle to change, and finally some of the very interesting directions this technique is taking us.

PROPOSED MECHANISMS

Blood flow restriction is the application of a surgical tourniquet to the proximal portion of the thigh or upper arm to reduce arterial inflow (Figure 3.1). The mechanisms driving skeletal muscle hypertrophy and strength adaptations to BFR-resistance exercise (BFR-RE) are not fully understood. It has been suggested that the ischemic and hypoxic muscular environment generated by BFR during exercise causes high levels of metabolic stress¹⁰ and mechanical tension. Similar to traditional heavy load-resistance exercise (HL-RE), metabolic stress and mechanical tension have been described as the primary factors related to hypertrophy adaptations. Blood flow restriction resistance exercise is also thought to act on other *secondary* mechanisms for the induction of muscle growth. The relative contributions of metabolic stress and mechanical tension may differ between HL-RE and BFR-RE. The HL-RE has resulted in greater mechanical tension and lower metabolic stress compared to BFR-RE, which may induce greater metabolic stress and less mechanical tension due to the light loads used during exercise. However, both metabolic stress and mechanical tension may have a synergistic effect on muscle hypertrophy during BFR-RE.

Additionally, it is plausible that either exercise modality activates similar mechanisms to drive muscle hypertrophy and strength adaptations and these occur in response to different stimuli. At present, the mechanisms proposed to explain these adaptations are mainly hypothetical and based on theoretical associations. Pragmatic and specific identification of these proposed mechanisms is currently lacking and requires further exploration, including their magnitude of involvement and the actual source of activation with BFR-RE.

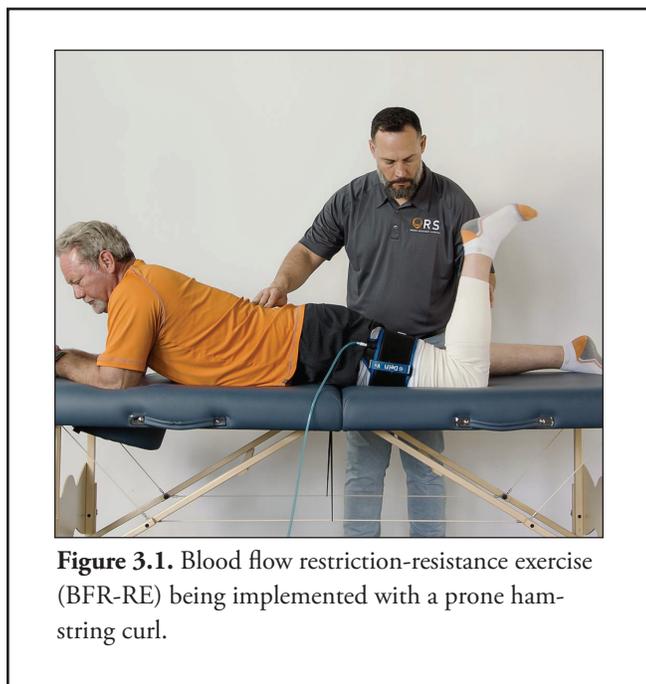


Figure 3.1. Blood flow restriction-resistance exercise (BFR-RE) being implemented with a prone hamstring curl.

Primary Mechanisms

Mechanical tension

A large body of evidence suggests that mechanical tension acts as a primary mechanism for muscle growth. Goldberg et al¹¹ first introduced the idea of mechanical *strain* on muscle and found it attenuated atrophy caused by unloading. This suggested mechanical tension was a critical factor initiating compensatory muscle growth. The mechanisms put forward by which mechanical tension induces muscle hypertrophy include mechanotransduction,^{12,13} increased local hormone production,¹⁴ muscle damage,¹⁵ reactive oxygen species production,^{15,16} and increased fast-twitch fiber recruitment.^{10,17,18} These all have been reported to increase protein synthesis through activation of signaling pathways,^{19,20} or satellite cell activation and proliferation⁵ for the induction of muscle growth. It has been suggested that BFR-RE results in low-level mechanical tension and thus does not induce these mechanisms to any great extent. However, metabolic stress has also been shown to mediate similar mechanisms, and therefore, the effects may be additive.

Metabolic stress

Metabolic stress, defined as an accumulation of muscle metabolites, has been identified as a critical driver of muscle growth.²¹ Mechanical loading and stretching of the muscle may also contribute to muscle hypertrophy.¹² Despite low mechanical forces during BFR-RE, the ischemic and hypoxic environment generated by BFR amplifies intramuscular metabolic stress.^{6,22} Blood lactate concentrations are higher following low-intensity resistance exercise performed under ischemic conditions such as BFR⁶ and hypoxia²³ compared with exercise performed under normal conditions. Also, direct relationships between other indices of metabolic stress (Pi and intramuscular pH) and muscle hypertrophy following BFR-RE has been reported in the literature.²² It is proposed that metabolic stress and mechanical tension act as primary drivers of hypertrophy, activating several secondary mechanisms during BFR-RE to promote skeletal muscle hypertrophy and strength adaptations. These secondary mechanisms include elevated systemic hormone production,^{6,24} cell swelling,²⁵ intramuscular anabolic/anti-catabolic signaling,²⁶⁻²⁸ and increased fast-twitch fiber recruitment.^{29,30}

As previously mentioned, the primary mechanisms act on several associated secondary mechanisms for the induction of muscle growth. The following sections will discuss these secondary factors concerning how they respond to BFR-RE.

Secondary Mechanisms

Systemic and local hormones

One popular theory proposed to explain the hypertrophic effects of BFR-RE is that the increased metabolic stress triggers a strong anabolic hormonal response post-exercise.⁶ Numerous studies have reported hyperbolic increases in systemic hormonal responses to BFR-RE, including an insulin-like growth factor-1 (IGF-1), growth hormone (GH),³⁰ and cortisol.²⁴ One partic-

ular study reported a 290-fold increase in plasma growth hormone response following an acute bout of BFR-RE.⁶ Although an amplified systemic anabolic endocrine response may occur, muscle hypertrophy appears to be isolated to the involved limb. West and Phillips reported increased myofibrillar protein synthesis in response to a resistance exercise protocol, independent of changes in the systemic levels of GH, IGF-1, and testosterone.³² Furthermore, Mitchell and colleagues found 16 weeks of resistance training increased muscle fiber cross-sectional area (CSA) of the vastus lateralis as well as strength, without any associated increases in GH, free testosterone, and IGF-1.³³

Cell swelling

A novel mechanism that may be involved in the hypertrophic adaptations of BFR-RE is the increase in intracellular hydration, known as *cell swelling*. Hydration-mediated cell swelling results in an increase in protein synthesis and a decrease in proteolysis in a variety of different cell types, including hepatocytes, osteocytes, and muscle fibers.³⁴ Increased accumulation of metabolites via BFR-RE induces a pressure gradient resulting in the flow of blood into the muscle fibers. The increased reperfusion and subsequent intracellular swelling are believed to threaten the structural integrity of the cell membrane,²⁷ causing the cell to initiate a signaling response that leads to a chronic reinforcement of its ultrastructure.^{12,36}

It is thought that signaling is carried out via integrin-associated volume osmosensors within cells.³⁷ These may activate molecular pathways associated with muscle protein synthesis, such as the mammalian target of rapamycin and mitogen-activated protein kinase. Additionally, it has been reported that cell swelling could also induce muscle growth through the proliferation and fusion of satellite cells.³⁸ Gundermann et al recently reported finding no significant increases in muscle protein synthesis following simulation of the reactive hyperemia response via a pharmacological vasodilator, suggesting that reperfusion may not be responsible for the hypertrophic adaptations of BFR-RE.³⁹ To date, the idea of cell swelling to explain the adaptations associated with BRR-RE is theoretical and likely to remain so, given the difficulty of measuring cell swelling in-vivo.

Muscle damage

Exercise-induced muscle damage (EIMD) is purported to be an essential regulator of satellite cell-mediated compensatory muscle growth.^{40,41} The greatest damage to muscle tissue is seen with eccentric exercise, where muscles are lengthened.⁴² Thus, support for the potential anabolic role of EIMD perhaps stems from studies that have reported the hypertrophic response⁴³ to be blunted when the eccentric phase is omitted from training. In addition, a meta-analysis by Roig et al proposed that eccentric training is superior to concentric training in mediating muscle hypertrophy.⁴⁴ On the other hand, the *repeated bout effect* suggests that despite one bout of eccentric exercise-induced muscle damage, repeated bouts of the same exercise have no

such effects,⁴⁵ which may contradict any association of EIMD with hypertrophy, because multiple exercise sets and chronic training are likely to lessen the muscle damage response. It is currently unclear whether EIMD plays a role in the adaptations of BFR-RE. Through the use of indirect markers, BFR-RE has been shown to induce minimal levels of damage.⁴⁶ In contrast, Umbel et al have reported EIMD by BFR-RE lasting for 48 hours.⁴⁷ Nonetheless, it is generally accepted that the low-level nature of BFR creates minimal EIMD. This is backed up by consistent reports of patients suffering nominal or no effects of EIMD such as delayed onset muscle soreness (DOMS). Thus, EIMD may not contribute to BFR-RE induced hypertrophy due to its low-intensity nature.

Muscle fiber recruitment

Though all these mechanisms may contribute to muscle hypertrophy, it is thought now that the biggest driver of muscle hypertrophy and strength adaptations is the early preferential recruitment of type II fast-twitch fibers at light loads due to the hypoxic muscular environment generated during BFR-RE. Typically, the high threshold motor units comprising fast-twitch muscle fibers are recruited only at high intensities of work. With BFR-RE, it appears this standard size principle of muscle recruitment is reversed.^{48,49} Several studies have demonstrated increased muscle activation during BFR-RE.^{50,51} Greater internal activation intensity has been found relative to an external load,^{30,52} which is greater than that observed in low-load training alone. In some cases, muscle activation during BFR-RE reportedly is similar to HL-resistance training.^{6,52} It appears that increased fast-twitch fiber recruitment is responsible for at least some of the hypertrophic adaptations seen with BFR-RE.

Autocrine and Paracrine Actions

Muscle growth ultimately is brought about by autocrine (eg, an increase in protein synthesis through increased anabolic and/or decreased catabolic signaling pathways) or paracrine (eg, increased satellite cell activation, proliferation, and fusion) actions. The two primary mechanisms act on associated secondary mechanisms that subsequently stimulate protein synthesis (autocrine) or satellite cell activity (paracrine) for the induction of muscle hypertrophy.

Autocrine: protein synthesis

The IGF-1/Akt signaling pathway plays a vital role in the regulation of muscle mass,^{20,53} and promotes muscle hypertrophy by stimulating overall protein synthesis and suppressing proteolysis. In skeletal muscle, activation of Akt by IGF-1 stimulates protein translation through the induction of mTOR, which is involved in the regulation of messenger-RNA translation initiation and plays a crucial role in exercise-induced muscle protein synthesis and hypertrophy.^{19,20,54} Blood flow restriction resistance exercise has also been shown to stimulate the mTOR signaling pathway via its associated downstream effectors (ribosomal S6 kinase 1 [S6K1] and ribosomal protein S6