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Cardiovascular, Neuromuscular, and Immune Responses and Adaptations to Blood Flow Restriction Training (BFR)

Abstract

Blood Flow Restriction Training (BFR) is an innovative training technique that has recently stupefied scientific research. Experiments continuously question the effectiveness of the phenomenon, which claims the ability to induce similar muscular hypertrophy and strength of higher-load resistance training, despite a resistance level of around 20-30% of an individual's 1RM (O'Halloran, 2014; Scott, 2016). The most crucial aspect of BFR is that an individual needs to be engaging in physical activity while restricted by some sort of wrapping device. These devices could be a cuff, elastic knee wrap, or more, as long as there's decreased blood flow to the recruited muscle (O'Halloran, 2014; Scott, 2016; Lixandrao, 2018). The restriction device should be placed at the upper arm and/or the upper thigh. Other positions on the body, such as the forearm or upper calf, may cause serious damage because of the superficial placement of nerves in those areas (O'Halloran, 2014; Scott, 2016; Lixandrao, 2018). The cuffing devices restrict venous return to the heart while maintaining arterial inflow during exercise (Laurentino, 2012; O'Halloran, 2014). The BFR concept stems from Kaatsu training, which was discovered by Dr. Sato in 1960's Japan, who noticed edema building in his body while kneeling, a similar sensation to what he experienced during high resistance training (O'Halloran, 2014; Lixandrao, 2018). BFR's hypertrophic results are provoked by the body's cardiovascular, neuromuscular, and immune responses to the restricted blood flow (O'Halloran, 2014; Silva, 2019; Cook, 2010; Hwang, 2019; Da, 2019). The personal, acute, physiological response to BFR exercise translates differently due to the overload or disuse an individual exposes themselves to on the regular (Scott, 2016).

Keywords

BFR; Cardiovascular System; Neuromuscular

Disciplines

Medicine and Health Sciences | Other Medical Sciences

Comments

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Cardiovascular, Neuromuscular, and Immune Responses and Adaptations to Blood Flow Restriction Training (BFR)

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Dr. Drury, HS 311
Final Research Project
Due: November 27, 2019
Neuromuscular Physiology

1. Hypothesis and Reasoning behind Blood Flow Restriction Training

Blood Flow Restriction Training (BFR) is an innovative training technique that has recently stupefied scientific research. Experiments continuously question the effectiveness of the phenomenon, which claims the ability to induce similar muscular hypertrophy and strength of higher-load resistance training, despite a resistance level of around 20-30% of an individual's 1RM (O'Halloran, 2014; Scott, 2016). The most crucial aspect of BFR is that an individual needs to be engaging in physical activity while restricted by some sort of wrapping device. These devices could be a cuff, elastic knee wrap, or more, as long as there's decreased blood flow to the recruited muscle (O'Halloran, 2014; Scott, 2016; Lixandrao, 2018). The restriction device should be placed at the upper arm and/or the upper thigh. Other positions on the body, such as the forearm or upper calf, may cause serious damage because of the superficial placement of nerves in those areas (O'Halloran, 2014; Scott, 2016; Lixandrao, 2018). The cuffing devices restrict venous return to the heart while maintaining arterial inflow during exercise (Laurentino, 2012; O'Halloran, 2014). The BFR concept stems from Kaatsu training, which was discovered by Dr. Sato in 1960's Japan, who noticed edema building in his body while kneeling, a similar sensation to what he experienced during high resistance training (O'Halloran, 2014; Lixandrao, 2018). BFR's hypertrophic results are provoked by the body's cardiovascular, neuromuscular, and immune responses to the restricted blood flow (O'Halloran, 2014; Silva, 2019; Cook, 2010; Hwang, 2019; Da, 2019).

2. Cardiovascular Responses and Adaptations

2.1 Heart Rate and Stroke Volume

Due to the compression during Kaatsu type training, there is a decrease in venous return to the heart, as well as a boost in vascular resistance and therefore afterload (Renzi, 2010; Da, 2019). In order to maintain homeostasis of the body and the stability of cardiac output, heart rate increases during BFR in comparison to non-restricted exercise, to combat stroke volume's shift (Renzi, 2010; Mahoney, 2019; Shimizu, 2016; Pope, 2013). H+ ions and Lactic acid plasma concentrations are on the rise during BFR, decreasing body pH to acidosis, which stimulates chemoreceptors to activate pressor reflexes. These reflexes inspire sympathetic activity (Renzi, 2010; Shimizu, 2016). Sympathetic nervous system activity showed more prominence in BFR than non-BFR resistance training, affirmed by heightened systemic levels of norepinephrine (Shimizu, 2016). There is a proposed relationship between the level of pressure of the BFR restriction device and the physiological response called upon: the higher the BFR pressure, the greater the change in heart rate and, consequently, stroke volume as well (Garten, 2019; Silva, 2019; Credeur, 2019).

2.2 Blood Pressure

Systolic blood pressure (SBP) and Mean Arterial Pressure (MAP) significantly increased in BFR exercise more than the opposing group (Silva, 2019; Shimizu, 2016). The resulting consequence of SBP, Diastolic Blood Pressure, and MAP also maintained a strong positive correlation with the level of intensity of the cuff. The increased pressure from the heart attempting to stabilize the venous return shortage leads to wall tension and increased systemic blood pressure, as well as changes in venous compliance (Garten, 2019; Abe, 2012; Da, 2019).

2.3 Cardiovascular Function and Cardiorespiratory Capacity

BFR enhances metabolic stress on the body. For example, a study observing 20 men who completed rowing exercises with BFR and control-non-BFR groups concluded that muscle oxygen saturation (Smo2) declined significantly during exercise, meaning the muscles consume more oxygen than they were delivered during BFR (Mahoney, 2019). Due to this, the body adjusts by improving cardiorespiratory capacity. This was observed in a study done on young adults, specifically basketball players, after cycling training over 2 weeks. Previous studies affirmed the same results of the increase in cardiorespiratory capacity, likely due to the body's adjustment in muscle oxidation. Cardiorespiratory capacity is plausibly tied to increasing muscle mass in the lower body and capillary density induced by the body's hypoxia, causing enhanced expression of growth factor hypoxia-inducible-factor-1 (HIF-1α) (Silva, 2019).

3. **Neuromuscular Responses and Adaptations**

3.1 Strength and Cross Sectional Area (CSA) Improvements

The venous occluded training technique delivers tangible improvements in strength and CSA, despite lower load (Scott, 2016; Mahoney, 2019; Abe, 2012; Lixandrao, 2018). A study was done on Division 1 Football athletes that were well-accustomed to anaerobic, high-intensity resistance training. The athletes replaced their workout regime with low-load BFR training a few times a week, and after the month long experimental period, they found that their 1RM for both bench press and squats had significantly increased in comparison to the control (non-BFR) group. Not to mention, there were physical differences in girth in upper and lower chest in the BFR group, but not in the thighs (Scott, 2016; Hwang, 2019). After an experiment observing walking exercise on elderly participants, incorporating BFR, it was found that muscle size improved, as well as carotid arterial and venous compliance (Abe, 2012). In low-intensity BFR knee extension exercise in young men, the synthesis of muscle proteins increased by 56%, while the control had no change (Abe, 2012). Many other studies have generated similar, positive results. But most importantly, BFR has proven to benefit the majority, to the whole body, instead of spot-hypertrophying. After occluded exercise, improved muscle activation and hypertrophy occurred in the trunk muscles, as well as other non-BFR muscles, because of their role in attempting to compensate for the force reduction (Abe, 2012; Hwang, 2019).

Similarly, over an 8 week preseason period of highly trained athletes, occlusion training compelled the mean improvements of training scores to drastically improve, incorporating bench press, squat, maximal sprint time, and countermovement-jump power (Cook et.al, 2014). The oxygen-deficient environment that venous occlusion training fosters in the body results in an increase in muscle strength due to motor unit recruitment, sympathetic nervous system stimulation, and inflated secretion of neurohumoral factors such as lactate, norepinephrine, growth factor, and vascular endothelial growth factor (VEGF) (Patterson, 2013; Shimizu, 2016; Cholewa, 2018). Frequently, external resistance manages fiber recruitment through Henneman's size principle, but BFR training responds to the intramuscular environment, such as metabolite accumulation's command (Lixandrao, 2018; Wilson, 2013).

3.2 Metabolite Accumulation and Endocrine Responses

Kaatsu type training challenges the body through metabolic stress, which incentivizes the endocrine response to release hormones and growth factors (GFs) (Fatela, 2019; Wilson, 2013). Despite the disparity in work-load between BFR and non-BFR methods, lactate and other metabolite accumulation proved venous occlusion drives anaerobic activity (Renzi, 2010; Shimizu, 2016; Wilson, 2013). In a particular study involving 65 healthy elderly volunteers, norepinephrine, lactate, epinephrine, and growth factors in the BFR group were significantly higher than the control, due to metabolic stress. Raised intracellular H+ ions and lactate to cause acidosis, which stimulates chemoreceptors in the body to communicate with the sympathetic nervous system to secrete growth hormone (GH), which possibly enhances hypertrophy (Renzi, 2010; Cook et.al, 2014; Shimizu, 2016). Also, the increased secretion of catecholamines in BFR groups aid in muscle growth, because of their role in dictating neutrophil demargination and magnitude of the lymphocyte response (Souza, 2019).

Increased secretions of hormones due to metabolite accumulations enhance the anabolic effect in the muscles, and assist in muscle protein synthesis, thus encouraging hypertrophy (Hwang, 2019). Hormones like GH, significant in occlusion training, are known to help regulate cell differentiation. GH aids in muscle protein synthesis, similar to Mechano Growth Factor, which responds to cellular damage and mechanical stimuli, most likely providing a mechanism for skeletal muscle hypertrophy that has thus far not been investigated deeply (Abe, 2012). Similarly BFR training is linked to increases in concentration of hormone-insulin-like growth-factor-1 (IGF-1), which improves muscle mass and strength by activating its muscle receptors to begin protein synthesis (Cook, 2010). The metabolite accumulation effect on the body is even more effective considering that BFR causes fatigue faster, generating a physiological immune response (Cook, 2010).

3.3 Motor Unit Recruitment and Fiber Selection

BFR training intrigued scientists, considering its anaerobic, fast twitch-fiber benefits. The vascular occlusion deprives the muscles of oxygen because of oxygen's presence in the blood. The low-load resistance, due to Henneman's size principle, would typically be handled by Type I fibers, equipped for aerobic activity. However, because of the forced hypoxia conditions, muscles cannot depend on the slow twitch fibers, because they cannot produce adequate force without reliable oxygen delivery, and are quick to fatigue. This ischemia causes additional motor unit recruitment, now involving Type II fibers, despite their high membrane potential, for a task they would not be introduced to before. The fast twitch fibers, rich in glycolytic enzymes and other adaptations to specialize in anaerobic metabolism, are activated to compensate for the lack of force development by the restricted Type I fibers. Electromyography studies confirmed the increase in recruitment of fast twitch fibers following Kaatsu-type training (Hwang, 2019; Cook, 2014; Fatela, 2019).

BFR's dependency on Type II then provides those fast twitch fibers overload. The strategic, forced fiber selection of BFR thus encourages an increase in CSA of Type II fibers (Hwang, 2019; Cook et.al, 2014). One specific study focusing on 1RM recorded a CSA improvement of 27.6% after two weeks in Type II fibers, and only an increase in 5.9% in slow twitch fibers (Hwang, 2019). Concentration of metabolites also connects with fiber recruitment. Metabolite accumulation stimulates group III and group IV afferent nerves, which then inhibit the alpha motor neuron that governs slow twitch fiber activity (Wilson, 2013). When compared, motor unit recruitment and firing rate have a linear relationship, but Electromyography reinforced that BFR decreased the linear slope coefficient of this relationship, meaning effective recruitment of motor units, despite their membrane potentials and firing rates (Fatela, 2019).

4. **Susceptibility to Muscle Damage and Rebuilding**

4.1 Muscular Failure and Delayed Onset Muscle Soreness (DOMS)

Moderate BFR, because of its effect on the internal environment of the body, focuses more on metabolic stress, swelling, and muscle activation, than brute force matching. Type II fibers won't experience the same mechanical stress or eccentric contraction to cause muscle damage or delayed onset muscle soreness (DOMS) (Fatela, 2019; Loenneke, 2012; Wilson, 2013). Systemic Plasma Creatine Kinase (CK) levels suggested the body's adjustment period, during the first BFR exercise session, is when the body is most prone to muscle damage (Nielsen, 2017). Once adjustment to the BFR regime occurs, disturbance of membrane permeability activates myogenic stem cell (MSC) activation and proliferation due to the release of growth factors (Loenneke, 2012; Nielsen, 2017). This sensitizes the body's response to micro-damage: an increased inflammatory response would follow acute exercise without the risk of muscular damage (Patterson, 2013; Loenneke, 2012; Nielsen, 2017).

Occluded low intensity exercise also provides a hypoalgesia affect through one, or a combination of these methods: Conditioned Pain Modulation (CPM), Exercise-Induced Metabolism (EIM), or high threshold motor unit recruitment (Hollander, 2010; Hughes, 2019). CPM is where pain inhibits pain by two noxious stimuli: the first stimulus triggers inhibition of extra-segmental spinal, and wide range neurons to reduce the perception of the second stimulus. CPM works with BFR to activate descending inhibitory pathways, but it is more likely that EIM is the main factor in BFR's hypoalgesia. EIM incorporates ATP, lactate, and protons that activate the dorsal root ganglion group III and IV nociceptive afferent neurons in skeletal muscle, which contribute to acute muscle pain to then induce CPM's mechanism (Hughes, 2019; Hollander, 2010; Fatela, 2019; Wilson, 2013).

4.2 Inflammatory and Immune Responses

Although BFR training is resistant to DOMS, slight disruption still needs to occur for the body to adapt to the overload and grow. This occurs by changes in volume, speed, flexibility, or intensity. Micro-tears in the muscle caused by Z-disk damage and/or sarcomere interruption eventually lead to decreased capability of the cytoskeletal matrix. Those physical changes are detected by mechanosensors, stretch-activated calcium channels, or transient receptor potential channels, which stimulate intracellular pathways to use mechanical energy as chemical communication to promote protein synthesis. Cytokines are also released by the activation of those channels and sensors, thus introducing the immune response to the muscle. Satellite and white blood cells are sent to the area to begin phagocytosis and muscle fiber rebuilding (Cholewa, 2018). As mentioned before, the body's state of hypoxia enhances expression of HIF-1α (Silva, 2019; Cholewa, 2018). HIF-1α increases presence of MCP-1, a chemokine known for macrophage recruitment. This, along with a higher release of catecholamines, namely norepinephrine, and increased levels of Interleukin-6 (IL-6), known for increasing neutrophil recruitment in skeletal muscle remodeling, are all possibilities of BFR's potent inflammation and immune response despite the absence of muscle damage (Souza, 2019; Cholewa, 2018).

4.3 Protein Signalling and Myostatin

Once the immune system responds and cleans up the area, whatever the degree of damage that occured, intracellular pathways and satellite cells take over to rebuild the muscle. Muscle protein synthesis is often done through activating the IGF 1-phosphoinositide-3-kinase-Akt/protein Kinase B-mammalian target of rapamycin (IGF1-P13K-Akt/PKB-mTOR) signalling pathway and by inhibiting myostatin (Cook, 2014; Hwang, 2019). The mTOR pathway is associated with decreasing proteolysis (Hwang, 2019). A study done on low-load resistance exercise with BFR found that there were increased levels of P38 Mitogen-Activated-Protein-Kinase (p-p38MAPK) in early post-exercise blood samples. This was an important finding, considering activation of p-p38MAPK often happens after skeletal muscle stretch (Wernbom, 2013). It is mainly phosphorylated after acute eccentric exercise, to stimulate the mTOR pathway (Hwang, 2019; Wernbom, 2013). P-p38MAPK is also associated with hypertrophy in some human cells (Wernbom, 2013).

Additionally, studies showed that 3 hours after BFR training, myostatin mRNA expression decreased, inducing muscle growth (Laurentino, 2012; Hwang, 2019). Over time, significant downregulation of myostatin gene expression occurred, even after 8 weeks of training. This is speculated to be because of BFR’s increased gene expression of GASP-1 and SMAD-7, inhibitors and managers of myostatin function. The lack of mRNA and myostatin, as well as the increase of the inhibitory factors further demonstrate BFR’s efficiency in activating hypertrophy (Laurentino, 2012; Hwang, 2019).

4.4 Swelling

Occluded training has resulted in an increase in muscle swelling. According to studies done in the past, cell swelling shifts protein balance into an anabolic state. BFR seemed to generate this swelling response in the body: venous pooling and fluid shifting into the muscle cells, from the vascular space into blood-flow restricted and non-restricted active muscles occurred. Fluid shifts are associated with a decrease in plasma volume after using Kaatsu wrapping devices, which then enable the body to transcend the anabolic intracellular signaling pathway. Cell swelling is also correlated with reduced proteolysis rates, which could cause an increase in protein balance and anabolism (Abe, 2012; Loenneke, 2012; Wilson, 2013). Although the direct mechanism is not yet confirmed, scientists speculate that the BFR exercise-induced swelling is detected by an intrinsic volume sensor that may lead to a G-protein-mediated activation of a type of tyrosine kinase, which leads to an activation of mTOR and MAPK signalling pathways, known to encourage hypertrophy (Cook, 2014; Loenneke, 2012; Abe, 2012).

4.5 Satellite Cells and Rebuilding

After venous occlusion training, satellite cell concentration per muscle fiber was observed to increase by 33-53% almost immediately (Hwang, 2019; Lixandrao, 2018; Wernbom, 2013). BFR, leading to recruitment of Type II fast twitch fibers, recruited inflammatory and endocrine responses, caused swelling, and inorganic phosphates, that regulate muscle protein signaling and increase satellite cell proliferation, leading to hypertrophy (Lixandrao, 2018; Wernbom, 2013; Cholewa, 2018).

5. **Disuse and Atrophy**

BFR is a convincing alternative to high intensity training, especially with limited populations. BFR, like high-load resistance training, can also counteract the effects of disuse on muscle atrophy (Cook, 2010). After 30 days of unloading in a study, muscle mass, strength, and endurance post-BFR resistance was preserved. However, despite its effectiveness with muscle mass and strength, neuromuscular dysfunction was not prevented (Cook, 2014; Cook, 2010). Other factors, like axonal nerve conduction velocity and neural alterations may have a strong tie to strength loss during disuse; not just atrophy (Cook, 2014). After observing several Unilateral

Lower Limb Suspension (ULLS) experiments, researchers concluded from one specific cause that the 8 participants not in BFR experienced a loss of 7.5% CSA and 16% strength throughout the course of the study, while BFR individuals only experienced 1% and 2% loss respectively (Cook, 2014). However, it is important to understand that consequences of disuse depends on the individual (Brandner, 2019). Even without perfect outcomes, BFR's resilience against disuse and atrophy is well demonstrated (Cook, 2014; Cook, 2010; Brandner, 2019).

6. **Practical Applications**

6.1 Benefits and Safety Concerns

BFR has less risk and cost on the body than other forms of resistance (Hollander, 2010; Scott, 2016). Occlusion training causes metabolic stress that encourages endothelial nitric oxide synthase (eNOS), which improves endothelial dysfunction in skeletal muscle vessels, thus enhancing blood flow, as well as peripheral blood circulation efficiency (Shimizu, 2016). BFR training is also proven to increase neuromuscular activation as well as its hypertrophic influence, becoming a countermeasure to prolonged disuse. Individuals involved in BFR were able to maintain force-generation capabilities and muscle mass after unloading. Consequently, BFR coupled with rehabilitation exercises drastically preserve those muscle characteristics more than just rehabilitation alone, meaning a major step forward in therapeutic techniques and recovery time post injury (Cook, 2014).

Although occlusion training has had a positive reputation thus far, it does pose risks. Disturbed blood flow has been observed to encourage endothelial activation, increasing circulating endothelial microparticles (EMP) and apoptotic endothelial cells. This is likely caused by hypoxia sending an injurious stimulus to endothelium in the body. People with atherprone arteries would be at a higher risk of this. EMP increase delivers inflammatory cytokines, carries regulatory microRNAs, decreases eNOS, and urges thrombosis, inflammation, and reactive oxygen species (ROS) production, all promoting endothelial dysfunction, and creating a positive feedback loop of vascular injury (Jenkins, N. T., 2013). The hemodynamic changes on the body possibly places strain on populations with compromised cardiac function, due to the inability to maintain cardiac output (Garten, 2019; Jenkins, 2013; Renzi, 2010). *Minor* occurrences of venous thrombosis, pulmonary embolism, and rhabdomyolysis have also surfaced. Although these are not common, it is important to approach BFR with caution (Jenkins, 2013; Hwang, 2019).

6.2 Targeted Populations

Venous occlusion training tends to benefit those that either don't have the resources or physical capacity to undergo high-intensity resistance training. For example, astronauts would benefit from BFR in order to prevent loss in muscular strength and disuse caused by microgravity unloading, because BFR is more accessible in small space vehicles (Mahoney, 2019). Occlusion training attracts injury-recovering, chronic health condition, and elderly individuals because of its low risk of muscle damage, lower mechanical stress, and minimal pressure on joints, in comparison to high intensity training (Abe, 2012; Hollander, 2010; Da, 2019; Clarkson, 2017).

7. **Future Research**

Moving forward, scientists must ask the question why BFR demands such a strong immune system response considering its lack of muscle damage (Cholewa, 2018). So far there hasn't been many negative effects of BFR training, however its long-term effects on strength, hypertrophy, and body systems are still unknown (Da, 2019; Wilson, 2013). Scientists might explore this by continuing to observe BFR on a *variety* of populations, especially ones that have not yet been explored, such as hypertensive, sarcopenic, osteoporotic, or diabetic individuals, and by measuring changing variables in the body such as circulating antioxidants, central activation, biomarkers of muscle damage, tissue necrotic factor (TNF), or potential markers of bone formation (Jenkins, 2013; Silva, 2019; Hwang, 2019; Cook, 2014; Credeur, 2019; Garten, 2019).

8. Conclusions

BFR is a method of training where upper arm or upper thigh cuffing during lighter load-exercise provides comparable gains and benefits to high intensity training. Evidently, BFR induces acute and chronic changes in the body's neuromuscular, cardiovascular, and immune systems, through manipulating metabolic and hemodynamic variables (O'Halloran, 2014; Silva, 2019; Hwang, 2019; Pope, 2013). Benefits change depending on the participant. For example, there is evidence to conclude that metabolic stress, due to change in phosphocreatine and intramuscular pH levels, was greater in aerobic athletes, like endurance runners (Pope, 2013; Scott, 2016). Meanwhile, anaerobic athletes weren't as metabolically challenged by the addition of BFR because they are less dependent on oxygen delivery during exercise. The personal, acute, physiological response to BFR exercise translates differently due to the overload or disuse an individual exposes themselves to on the regular (Scott, 2016).

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Note:

- Cook, C. J., 2014= Cook et.al, 2014 **VS** Cook, S.B., 2014= Cook, 2014