Acute Effects of a Resistance and Aerobic Intervention with Blood Flow Restriction on Vasodilation, Blood Flow and Muscle Oxygenation in Young Adults

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ABSTRACT

Acute Effects of a Resistance and Aerobic Intervention with Blood Flow Restriction on Vasodilation, Blood Flow and Muscle Oxygenation in Young Adults

Angelika Gnanapragasam

Blood flow restriction (BFR) training, a technique combining low intensity exercise with blood flow occlusion, has been shown to be safe and effective in eliciting gains in muscle mass and strength across multiple populations including athletes and rehabilitating individuals. Benefits such as producing less muscle damage leading to faster recovery after training and the deterrence of muscular atrophy after surgery have made this an increasingly popular technique. Currently, much of the literature has probed the long-term effects of BFR on the human body, often testing participants over a few weeks or months. Despite this, little is still known about the immediate effects of BFR. A study was conducted to examine the acute effects of BFR on a young and healthy population. Chapter 1 provides theoretical context to this project and examines the current literature. Chapter 2 describes the study that was conducted to gain greater insight into the acute effects of BFR training, specifically looking at the effects on vasodilation, blood flow and muscle oxygenation. Lastly, chapter 3 includes a conclusion and future research directions.

Keywords: Blood flow restriction, vasodilation, blood flow, muscle oxygenation, acute effects

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CONTRIBUTION OF AUTHORS

Angelika Gnanapragasam obtained ethics approval, recruited participants, collected data, carried out the data and statistical analysis, and wrote the thesis. This was accomplished with Dr. Andreas Bergdahl who helped significantly in designing the study, collecting data, providing access to facilities and equipment, and offering essential feedback on the ethics form, statistical analysis and the thesis. Furthermore, Angelika Gnanapragasam and Dr. Andreas Bergdahl worked together in troubleshooting the study protocol in its early stages and perfecting various data collection techniques such as the ultrasound measurements.

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ABBREVIATIONS

ANOVA… .... Analysis of variance

AOP ....Arterial occlusion pressure

BFR .... Blood flow restriction

BFR-A… .... Blood flow restriction and aerobic exercise

BFR-R .... Blood flow restriction and resistance exercise

eNOS .... Endothelial nitric oxide synthase

FMD… .... Flow-mediated dilation

GH .... Growth hormone

HIRT… ....High intensity resistance training

IGF……………………………………………………………….... Insulin-like growth factor-1

LIRT… .... Low intensity resistance training

NIRS...Near-infrared spectroscopy

NO .... Nitric oxide

OBLA… .... Onset of blood lactate accumulation

PI .... Principal investigator

SBP..Systolic blood pressure

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CHAPTER 1. THEORETICAL CONTEXT

1.1 Why Blood Flow Restriction?

The positive health outcomes of exercise being emphasized to physicians in Canada has led to a 20% to 74% increase of physical activity prescription to patients (Fowles et al., 2018). This is much warranted as research has shown that a lack of physical activity leads to an increased risk of a variety of health conditions such as obesity, type 2 diabetes, osteoporosis, coronary heart disease, stroke, cancer, depression and anxiety (Ruegsegger & Booth, 2018). Exercise presents a natural, low-cost solution to treat and prevent a number of health conditions that may otherwise be remedied with procedures and drugs that pose adverse side effects.

Often, the populations who benefit from exercise the most seem to have the greatest barriers. A focus group study by Lees et al. (2005) identified the greatest obstacle among non-exercising older adults as the fear of injury. This is also seen among rehabilitating athletes and brings about detrimental effects such as decreased sports participation and poor rehabilitation outcomes (Hsu et al., 2017).

Blood flow restriction (BFR) training has become an excellent solution to overcoming this common barrier. This technique has been shown to be safe and effective in eliciting gains in muscle mass and strength across multiple populations. First seen in Japan with Dr. Yoshiaki Sato and termed "KAATSU training", this technique involves the use of a specialized cuff to partially occlude blood flow in the extremities during low-intensity exercise (Patterson, Hughes, Warmington, et al., 2019). It has since grown in popularity in the athletic setting and is being widely researched to understand the related physiological mechanisms as well as its effects on populations like older adults and rehabilitation patients (Sato, 2005).

1.2 Physiological Mechanisms of BFR

BFR when combined with low intensity resistance training (LRT) (i.e. BFR training) has similar effects to that of high intensity resistance training (HRT) (Takarada et al., 2000). To understand what equates BFR training to regular HRT, it is important to examine how the BFR cuff affects the vasculature and muscles. The pressure applied by BFR causes arterial inflow to be partially restricted while venous outflow is more heavily restricted (Patterson, Hughes, Warmington, et al., 2019). The partial restriction of blood flow initiates a transient state of hypoxia within the muscles that is conducive to muscle growth such as in high intensity exercise (Biazon et al., 2019). In other words, although BFR training lacks the high mechanical tension typically required for muscle growth, the increased metabolic stress compensates by stimulating muscle protein synthesis (Biazon et al., 2019). This explains why combining BFR with HRT does not produce additional benefits; the muscles are already subjected to high mechanical tension (Biazon et al., 2019).

On the other hand, the partial blockage of blood flow also causes local accumulation of metabolites such as lactate (Madarame et al., 2007). As the contraction of muscle is inhibited by lactate buildup, there is an increased activation of the motor units (Teramoto & Golding, 2006). Additionally, the lactic acid (which constitutes lactate and hydrogen ions) stimulates group III and IV afferent nerves (Figure 1) (Teramoto & Golding, 2006). The body, consequently, responds to these events with the release of growth hormone (GH), testosterone and insulin-like growth factor-1 (IGF-1) (Madarame et al., 2007). These are anabolic hormones that are known to play key roles in the muscle building pathway (Madarame et al., 2007). GH levels in the blood, in particular, have been shown to significantly increase with BFR training, with one study by Pierce et al. (2006) even demonstrating a ninefold increase over baseline values. Significant increases in GH concentrations can also be seen during HRT (Seo, So & Sung, 2016).

Numerous studies have been conducted to demonstrate the effects of these mechanisms, with increased hypertrophy and strength being among the most extensively researched outcomes. Vechin and colleagues (2015), for instance, carried out a 12-week training program on the quadriceps with older adults that revealed HRT increased muscle cross sectional area by 7.9% followed closely by BFR training that grew by 6.6%. Furthermore, the increase in muscle strength was demonstrated in a study by Biazon et al. (2019) where HRT and BFR training caused significant increases of 41.0% and 32.2% respectively after 10 weeks of resistance training.

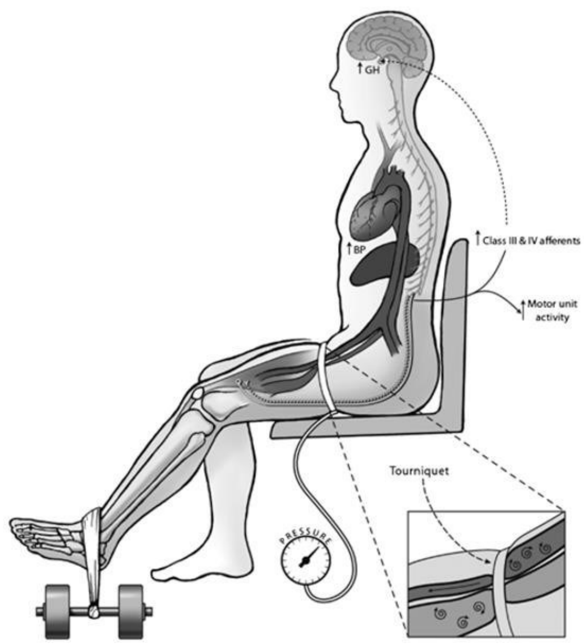

Figure 1. The effect of blood lactate buildup on the body during BFR training (adapted from Manini & Clark, 2009)

1.3 BFR Training Within an Athletic Context

Healthy athletes are among the many who have benefited from BFR training. Within this group, coaches and trainers have effectively enhanced sports performance through the application of BFR (Pignanelli et al., 2021). For instance, BFR training proved to be helpful when used in addition to taekwondo training to increase dynamic balance and strength (Akin & Kesilmis, 2020). This outcome is beneficial for these athletes as rapid kicking and direction changes, motions that are common in taekwondo, rely heavily on the strength and balance abilities of the athlete (Akin & Kesilmis, 2020). In this same way, an increasing number of studies have shown that using BFR with specific exercises improve basic motions that are common in most sports. An example of this is performing lunge exercises with BFR to improve subsequent vertical jump performance with post-activation potentiation elicited by the BFR (Doma et al., 2020). This is an extremely useful outcome as jumping is typically seen in many sports such as volleyball, basketball, tennis, gymnastics and handball.

In addition to BFR being useful to athletes in developing specific skills, incorporating BFR into an athlete's training protocol has been shown to produce less muscle damage and inflammation, allowing for faster recovery after the training (Loenneke et al., 2014). This would allow athletes to train more frequently within a shorter period of time. For example, as many as 12 BFR training sessions over only 6 days increases muscle strength and hypertrophy (Fujita et al., 2008). These results are similar to studies that executed longer training sessions with higher intensity or volume (Fujita et al., 2008). This level of efficiency is highly attractive for athletes that may be looking to get ahead of their opponents. From a more practical standpoint, it can benefit student athletes who often are balancing busy schedules.

BFR training has also been implemented among varying types of athletes. The differences in benefits experienced with BFR training is particularly interesting when comparing strength trained athletes vs endurance trained athletes. The former, such as boxers, powerlifters, or wrestlers, may experience increases in the amount of myonuclei, in muscle size, and in type I muscle fibers when compared to traditional HRT alone (Bjornsen et al., 2018). The observed myonuclear response allows for greater protein synthesis within the cytoplasm of the cell, further promoting muscle hypertrophy (Bjornsen et al., 2018). As well, the increase in type I fibers is beneficial as strength trained athletes tend to predominantly develop type II fibers due to the nature of their sport. It should be noted that there is also evidence suggesting that BFR training can increase both type I and type II muscle fibers (Nielsen et al., 2012).

When considering the benefits experienced by endurance trained athletes, it is important to understand how performance in these types of athletes is measured. Measurements in VO_2max and onset of blood lactate accumulation (OBLA) are often considered in weighing performance among endurance trained athletes (Smith et al., 2022). VO_2max depicts the maximum uptake of oxygen during intense exercise and is, consequently, high in elite athletes (Joyner & Coyle, 2008). OBLA refers to the point at which lactate concentrations begin to increase in the bloodstream due to the body's inability to keep up with the rate of glycolysis within the exercising muscles (Joyner & Coyle, 2008). Endurance athletes often aim to enhance their performance by increasing their VO_2max and delaying the OBLA to a higher percentage of their VO_2max. (Joyner & Coyle, 2008). These two factors can be improved through low to moderate intensity endurance training (Smith et al., 2022). However, among already trained athletes, improvements do not come as easily as with untrained individuals (Smith et al., 2022).

Fortunately, training with BFR has been shown to improve VO_2max and OBLA within endurance trained athletes (Smith et al., 2022). For example, one study by Chen and colleagues (2022) showed greater increases in VO_2max (5.1% vs -1.1%) in this type of athlete when comparing a group who performed 8 weeks of running training with BFR to a group who completed this same training without BFR. This same trend is seen when looking at OBLA, where improvements can be seen depending on the method of BFR application, i.e. continuous or intermittent application (Smith et al. 2022). The latter refers to the inflation of the BFR cuff during exercise and its deflation in between repetitions whereas the former refers to the technique being applied throughout (Corvino et al., 2017). Moreover, these athletes are not excluded from experiencing many of the same benefits as resistance athletes such as muscle strength and hypertrophy (Chen et al. 2022)

1.4 BFR as a Rehabilitation Technique

Perhaps the most common use for BFR is within the context of rehabilitation. As of 2021, close to 60% of orthopaedic surgeons reported using BFR in their practice with about 75% having implemented this technique within the last 1-5 years (Castle et al., 2023). Among those who did not use BFR, a third reported having the intention to begin using it in the future (Castle et al., 2023).

Professionals in rehabilitation may use this technique to build muscle while avoiding the stress that may be put on joints and connective tissue, which is of particular importance post-operatively (Vopat et al., 2020). For example, individuals who have undergone ACL reconstruction surgery may greatly benefit from BFR training within the months it takes for the ligament to mature enough to bear a load (Jack et al., 2023). By incorporating BFR into the rehabilitation program, patients may produce a greater recovery of strength and a decrease in loss of muscle as compared to not incorporating BFR (Jack et al., 2023).

Additionally, BFR training can be used post-operatively to deter the muscular atrophy that can ensue following an operation or injury (Vopat et al. 2020). Interestingly, it can be applied either passively or during exercise to accomplish this goal (Patterson, Hughes, Owens, et al., 2019). Passive BFR, specifically, has been shown to decrease weakness in the muscle caused during periods of limb immobilization (Kubota et al., 2011). Rehabilitation professionals may reach this outcome with their patients using a BFR cuff pressure as low as 50 mmHg (Kubota et al., 2011). The mechanisms behind these results have yet to be fully understood warranting further research.

Moreover, pain reduction is another reason why rehabilitation professionals may consider using BFR. A study by Fan and colleagues (2023) showed significantly decreased pain levels when BFR was incorporated into the rehabilitation intervention following surgery in the upper extremity. This contributed to improved functionality among these patients compared to those who went through a regular training regimen with no BFR (Fan et al., 2023). These reported effects may be, in part, due to the activation of the opioid and endocannabinoid systems during low-intensity BFR exercise (Hughes & Patterson, 2019). Both of these systems produce hypoalgesic effects triggered by an acute pain perception induced by the stimulation of group III and IV afferent fibres and the sympathetic nervous system (Hughes & Patterson, 2019). Additionally, stemming from the high metabolic stress caused by BFR training, a phenomenon known as Conditioned Pain Modulation may also be triggered in the same way as the opioid and endocannabinoid systems (Hughes & Patterson, 2019). Finally, a third potential mechanism to the pain reduction caused by BFR training may come from the early stimulation of high threshold motor units (Hughes & Patterson, 2019). Normally, this occurs during prolonged periods of high intensity exercise (Henneman et al.,1965). However, due to the muscle hypoxia caused by BFR, this activation occurs sooner (Pearson & Hussain, 2015). In short, because BFR training mimics the effects of high intensity exercise, many of the same pain reducing mechanisms are present.

Lastly, as BFR application is simple, it may easily be incorporated into an at-home rehabilitation program. With enough instruction and monitoring from professionals, this technique has been seen as an inexpensive way to bring about rehabilitation outcomes (Kilgas et al., 2019). For instance, when patients undergo ACL reconstruction surgery, it may leave them with residual quadriceps muscle impairments along with muscle asymmetry even years after the surgery (Kilgas et al., 2019). A home-based BFR program has been shown to produce increased muscle symmetry, strength and physical function (Kilgas et al., 2019).

1.5 Flow-Mediated Dilation to Assess the Effects of BFR

Flow-mediated dilation (FMD) is a physiological process that is used to assess the ability of a conduit artery to dilate after a period of increased blood flow and, consequently, increased shear stress (Stout, 2009). It has been shown to be a predictor of cardiovascular events among patients with cardiovascular diseases including coronary artery disease, acute coronary syndrome, chronic heart failure, and peripheral vascular disease (Thijssen et al., 2011). FMD has also been shown to help predict cardiovascular events in individuals who are asymptomatic and better classify them as being low, intermediate or high risk for these events (Yeboah et al., 2009). Furthermore, FMD also produces insightful prognostic data. Rossi and colleagues (2008) studied this by observing more than 2000 post-menopausal females for cardiovascular disease and concluded that when FMD was taken into account, it was a better predictor of cardiovascular events than traditional risk factors. Therefore, this physiological process has been widely used in studies to better understand how vascular and endothelial function may be affected through chronic or acute stimuli such as smoking or exercise (Thijssen et al., 2011). For instance, Neunteufl and colleagues (2000) used the change in FMD to demonstrate how vitamin E consumption in heavy smokers brings about the transient attenuation of endothelial function impairment.

On a physiological level, FMD is generally understood to be caused by the release of a number of vasodilators by the vascular endothelium (Harris et al., 2010). Endothelial cells, found in a single layer lining blood vessels, open specialized ion channels when stimulated by blood flow-associated shear stress (Figure 2) (Stout, 2009). These channels increase the calcium concentration inside of the cell, activating endothelial nitric oxide synthase (eNOS) (Stout, 2009). This leads to the production of nitric oxide (NO), the main vasodilator responsible for FMD (Harris et al., 2010). Other vasodilators include prostacyclin and endothelium-derived hyperpolarizing factor (Vanhoutte & Mombouli, 1996). Nitric oxide, once diffused from the cell and into the nearby smooth muscle, will trigger the dilation of the blood vessel (Thijssen et al., 2011). In this way, NO bioavailability is a marker for cardiovascular disease risk (Stout, 2009).

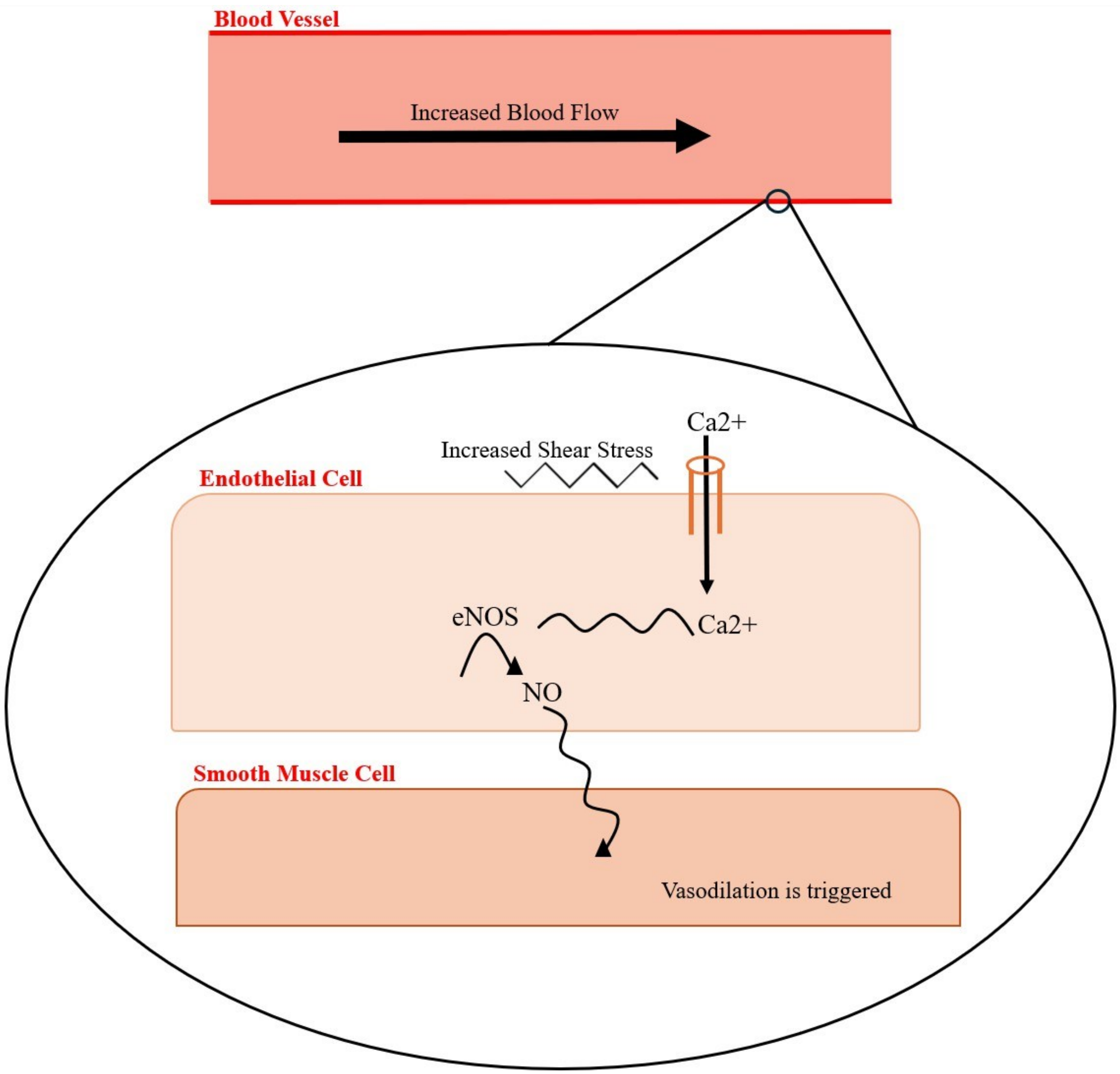

Figure 2. The cascade of events (simplified) leading to vasodilation triggered by nitric oxide (NO).

Specifically, FMD may be initiated by one of two methods: active hyperemia or reactive hyperemia. Active hyperemia refers to the increase in blood flow caused by increased metabolic activity such as exercise (Padilla et al., 2006). Reactive hyperemia refers to the increase in blood flow due to the body's response to a lack of blood flow which can be caused by events such as

BFR (Padilla et al., 2006). Both of these methods are useful in clinical studies. For example, active hyperemia has been used to investigate the role and differences of muscle perfusion during muscle fatigue between males and females (Hunter et al., 2006). Similarly, Duffy and colleagues (2001) used reactive hyperemia to study the reversing effects of black tea consumption on endothelial dysfunction in individuals with coronary artery disease. However, active and reactive hyperemia have been especially useful in investigating BFR, often showcasing the positive effects of the technique on a variety of populations such as older adults, healthy young males, and even overweight young adult females (Shimizu et al. 2016; Zhao et al., 2021; Bond et al., 2017). Therefore, FMD is a practical and insightful tool used to examine the effects of BFR.

CHAPTER 2. MANUSCRIPT

Acute effects of a resistance and aerobic intervention with blood flow restriction on vasodilation, blood flow and muscle oxygenation in young adults

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This crossover study was conducted with 30 healthy young adults between the ages of 18-35. Testing occurred under these conditions: No BFR (Control), with BFR, with BFR and resistance exercise (BFR-R), with BFR and aerobic exercise (BFR-A). Measurements for vasodilation, blood flow and muscle oxygenation were taken through ultrasound imaging and near-infrared spectroscopy (NIRS). Significant changes in vasodilation, blood flow and muscle oxygenation were observed. Additionally, strong correlations between blood flow and vasodilation ($r = 0.474$) as well as blood flow and muscle oxygenation ($r = -0.562$) were seen. The type of exercise used with BFR did not affect the influence BFR training had on blood flow and muscle oxygenation. In conclusion, vasodilation, blood flow and muscle oxygenation are affected within the first minute of BFR application. These changes suggest that the roles of active and reactive hyperemia are highly influential in bringing about changes to the body through BFR.

Keywords: Blood flow restriction, vasodilation, blood flow, muscle oxygenation, acute effects

2.1 Introduction

Originating in Japan, blood flow restriction (BFR) training has grown in popularity and is being widely researched to better understand the underlying physiological mechanisms (Sato, 2005). BFR training combines low intensity exercise with partial blood flow occlusion in the upper or lower extremities. This has been shown to be safe and effective in eliciting gains in muscle mass and strength across multiple populations including athletes and rehabilitating individuals (Pignanelli et al. 2021; Lorenz et al. 2021). Performed with a specialized cuff or tourniquet positioned proximally on the limb, BFR results in the partial restriction of arterial flow and a complete restriction of venous flow, initiating a transient state of hypoxia within the muscles that is conducive to growth such as in high intensity exercise (Patterson, Hughes, Warmington, et al., 2019; Biazon et al., 2019). Therefore, the increased metabolic stress in BFR training compensates for the lack of high mechanical tension by stimulating muscle protein synthesis (Biazon et al., 2019).

Incorporating BFR into an athlete's training has been shown to produce less muscle damage and inflammation, leading to faster recovery (Loenneke et al., 2014). A study by Fujita and colleagues (2008) demonstrates the benefits of this faster recovery by showing that as many as 12 BFR training sessions over only 6 days increases muscle strength and hypertrophy, producing results that are similar to that of longer training sessions with higher intensity or volume. In addition to this, studies have shown how BFR training is comparable to traditional high intensity training (Vechin et al., 2015; Biazon et al., 2019 Bjornsen et al., 2018). This level of efficiency is highly attractive for athletes that may be looking to get ahead of their opponents.

Perhaps the most common use for BFR is within the context of rehabilitation. As of 2021, close to 60% of orthopaedic surgeons reported using BFR in their practice with about 75% having implemented this technique within the last 1-5 years (Castle et al., 2023). The increasing popularity of BFR training is justified as it holds a great number of benefits for the rehabilitating individual. For example, this technique can help patients post-operatively to build muscle while avoiding the stress that may be put on joints and connective tissue (Vopat et al., 2020). Additionally, although yet to be fully understood, BFR used either passively without exercise or during exercise has been seen to deter muscular atrophy following an operation or injury (Patterson, Hughes, Owens, et al., 2019; Vopat et al. 2020). Passive BFR, which entails the inflation of the BFR cuff without any exercise, specifically, has been shown to decrease weakness in the muscle caused during periods of limb immobilization (Kubota et al., 2011). Moreover, accounting for the decreased pain levels and thus improved functionality from BFR training, as well as its inexpensive and simple application to be incorporated into an at-home rehabilitation program, this technique is an obvious option in clinical practice (Fan et al., 2023; Kilgas et al., 2019).

Flow-mediated dilation (FMD) is a physiological process that is useful in investigating BFR, often showcasing the positive effects of the technique on a variety of populations (Shimizu et al. 2016; Zhao et al., 2021; Bond et al., 2017). FMD assesses the ability of a conduit artery to dilate after a period of increased blood flow and, consequently, increased shear stress (Stout, 2009). This increase in blood flow can be initiated by elevated metabolic activity (active hyperemia) or as a result of the body's response to a lack of blood flow (reactive hyperemia) (Padilla et al., 2006).

The efficiency of BFR training suggests that physiological changes may be occurring sooner and with less effort with BFR than with traditional high intensity exercise. However, despite the vast amount of studies conducted on BFR, little is still known about its immediate effects. Much of the current literature has only probed the long-term effects of BFR, often testing participants over a few weeks or months. Analyzing the acute impact of BFR is, therefore, warranted to better understand its full effects and make it safer for all populations. Thus, the objective of this study was to gain greater insight into the acute physiological effects of BFR training, particularly on vasodilation, blood flow and muscle oxygenation in the brachial artery.

2.2 Methods

2.2.1 Study Design & Participants

This crossover study recruited thirty young adults (24.60 years ± 3.73) by word of mouth and advertisements at a local university campus after the Certification of Ethical Acceptability for Research Involving Human Subjects was received (Appendix Table 1). Potential participants contacted the principal investigator communicating their interest and, consequently, received the informed consent form along with a baseline questionnaire to deem participant eligibility (Appendix Table 2). Once screened, participants were scheduled for the testing session totaling 45 minutes. As this was a crossover design, participants were used as their own controls and were tested with both aerobic and resistance BFR exercise. Participant or evaluator blinding was not possible for this study.

2.2.2 Intervention

Each testing session involved the following conditions: No BFR (Control), with BFR, with BFR and resistance exercise (BFR-R), with BFR and aerobic exercise (BFR-A). Testing was carried out on the participant's left arm (Appendix Figure 1). BFR was administered using the Hokanson E20 Rapid Cuff Inflator and the pressure of the cuff was set at 80% of the participant's resting systolic blood pressure (May et al., 2017; Patterson, Hughes, Warmington, et al., 2019). Resistance exercise was done using the Camry EH101 electronic hand dynamometer to produce and monitor an isometric contraction of the forearm muscles while aerobic exercise was carried out with a rubber ball pumped at 100bpm controlled by a metronome. Ultrasound imaging (Samsung H60 with a 12MHz linear probe) was used to assess vasodilation of the brachial artery in combination with the Doppler function to identify blood vessels. Ultrasound measurements were collected in the form of 6 second videos. Near-infrared spectroscopy (NIRS) was carried out through a MOXY Monitor placed atop the forearm muscles to collect and provide live measurements of blood flow and muscle oxygenation.

Ultrasound measurements were collected at each testing condition while NIRS data was gathered continuously throughout the entirety of the session. Between the BFR-R and the BFR-A conditions, participants were asked to rest for 10 minutes. This acted as a "washout period", allowing the blood flow and tissue metabolism to return back to normal before testing the next condition. A second washout period occurred after the completion of the final testing condition. Furthermore, BFR-A and BFR-R were alternated randomly between participants (Appendix Figure 2).

2.2.3 Data Collection Procedures

Participants were instructed to arrive wearing a t-shirt, avoid intense exercise and avoid drinking coffee at least 3 hours prior to the testing session. Upon arriving to the testing session, participants were asked to be seated and remain at rest for at least 15 minutes before blood pressure was taken and used to calculate BFR cuff pressure. The participant was then guided on completing each testing condition (Table 3).

Control	One ultrasound measurement was taken after the participant was seated for at least 15 minutes.
BFR	The participant was asked to remain at rest and had the BFR cuff turned on. After 1 minute, the BFR cuff was turned off and two ultrasound measurements were taken, once right before the cuff was turned off and once immediately after.
BFR-R	The BFR cuff was turned on and the participant was asked to squeeze and hold a hand grip dynamometer at their maximum strength for 1 minute. After the completion of 1 minute of exercise, the cuff was turned off. Two ultrasound measurements were taken, once right before the cuff was turned off and once immediately after.
BFR-A	The BFR cuff was turned on and the participant was asked to squeeze a stress ball for 1 minute at a speed of 100 beats per minute, following the sound of a metronome. After the completion of 1 minute of exercise, the cuff was turned off. Two ultrasound measurements were taken, once right before the cuff was turned off and once immediately after.

Table 3. Details of the four testing conditions that each participant underwent

2.2.4 Data Analysis

Vasodilation recorded through the 6-second ultrasound video clips produced images of size fluctuations of the brachial artery. The change in circumference and area was then calculated using a computer software known as MicroDICOM. Muscle oxygenation and blood flow recorded in the form of detailed digital line graphs were analyzed by the time points of each testing condition.

Normality was confirmed using the Shapiro-Wilk test. Exploratory analysis provided the mean and mode for vasodilation, blood flow and muscle oxygenation. Once normality of data was confirmed, a one-way repeated measures analysis of variance (ANOVA) with the Bonferroni post-hoc test was conducted to analyze the effects of different types of training (Control, BFR only, BFR-A and BFR-R) on vasodilation. This post hoc test was chosen to control for Type 1 errors and was appropriate for the small sample size of this study. This same process was repeated for blood flow and muscle oxygenation. A Grubb's test was conducted with all raw data points in vasodilation, blood flow and muscle oxygenation. Statistical analysis was conducted with SPSS Statistics (v29, IBM).

2.3 Results

2.3.1 Vasodilation

Aerobic exercise in combination with BFR showed a greater percent change in brachial artery area (~20%) from the Control than BFR alone (~12%) or BFR with resistance exercise (~8%) (Appendix Figure 3). Moreover, although BFR-R appeared to have the smallest change in comparison to all other testing conditions, the percent change during the recovery phase of BFR-R still closely matched that of the aerobic exercise.

There were no statistically significant effects of the testing conditions on the circumference of the brachial artery ($p=0.053$), however, there were significant effects on the cross-sectional area ($p=0.017$). Specifically, there were statistically significant differences between the Control and BFR conditions ($p=0.044$) as well as the Control and Post BFR-A conditions ($p=0.009$). Of note, a Grubb's test conducted prior to this revealed an outlier among the BFR-A area data set. When this outlier was removed, the repeated measures ANOVA continued to show statistically significant results among the data ($p=0.041$). However, the subsequent post hoc test revealed a significant difference between the Control and Post BFR-A conditions ($p=0.019$) only. Finally, vasodilation was measured for each participant, however, technological issues caused data in the BFR-R condition to be lost for one participant.

	N	Percent Change of Area *Mean (SD)*	Percent Change of Circumference *Mean (SD)*
BFR	30	11.79 (19.97)*	6.95 (9.56)
BFR-A	30	20.11 (30.79)	7.78 (15.35)
Post BFR-A	30	21.70 (29.06)*	9.51(13.90)
BFR-R	29	8.21 (42.68)	3.82 (19.19)
Post BFR-R	30	20.43 (37.11)	8.26 (16.10)

Table 4. Percent change of area and circumference during each condition compared to control.
*Statistically significant $p<0.05$

2.3.2 Blood Flow

Total blood flow increased during all 3 testing conditions (Appendix Figure 4). BFR when combined with exercise (i.e. BFR-A and BFR-R) produced the greatest increase in blood flow. Significant differences were noted between Control and BFR ($p<0.001$), Control and BFR-A ($p<0.001$), Control and BFR-R ($p<0.001$), BFR and BFR-A ($p=0.005$) and BFR and BFR-R ($p<0.001$). No statistically significant differences were observed between BFR-A and BFR-R conditions ($p=1.000$). Finally, there was a less than 1 % increase in blood flow at the post BFR-A and post BFR-R stage when compared to Control (Appendix Figure 5).

	Total Blood Flow *Mean (SD)*
Control vs BFR	0.57 (0.68)
Control vs BFR-A	1.53 (1.79)
Control vs BFR-R	1.70 (1.65)
BFR vs BFR-A	0.96 (1.40)
BFR vs BFR-R	1.13 (1.39)

Table 5. Mean percent change of blood flow in the brachial artery during each testing condition

2.3.3 Muscle Oxygenation

Oxygenation of the forearm muscles decreased under all 3 testing conditions with the greatest decrease seen with the presence of exercise (Appendix Figure 6). There was a statistically significant difference between Control and BFR-A ($p<0.001$), Control and BFR-R ($p<0.001$), BFR and BFR-A ($p=0.014$), BFR and BFR-R ($p=0.001$). No significant difference was reported between Control and BFR ($p=0.126$) and BFR-A and BFR-R ($p=1.000$). Lastly, trends showed slight increases from Control in muscle oxygenation as the body recovered after BFR exercise (Appendix Figure 7).

	Muscle Oxygenation *Mean (SD)*
Control vs BFR	-4.59 (8.69)
Control vs BFR-A	-13.63 (15.42)
Control vs BFR-R	-16.33 (18.38)
BFR vs BFR-A	-8.73 (18.96)
BFR vs BFR-R	-11.76 (20.77)

Table 6. Mean percent change of muscle oxygenation in the brachial artery during each testing condition.

2.3.4 Correlated Effects Between Outcomes

Correlations have been observed between blood flow and muscle oxygenation ($\alpha=0.01$; $p=0.001$; $r= -0.562$) (Appendix Figure 8), as well as blood flow and vasodilation ($\alpha=0.01$; $p=0.008$; $r= 0.474$) (Appendix Figure 9) during the BFR testing condition. Additionally, there is a correlation between blood flow and muscle oxygenation during the BFR-A ($\alpha=0.05$; $p=0.023$; $r= -0.414$) (Appendix Figure 10) and the BFR-R ($\alpha=0.01$; $p<0.001$; $r= -0.590$) (Appendix Figure 11) testing conditions.

2.4 Discussion

The objective of this study was to gain insight into how vasodilation, blood flow and muscle oxygenation were acutely affected by BFR training. The present study is the first to look at the immediate effects of BFR on vasodilation, blood flow and muscle oxygenation. The main findings include:

- significant increases in vasodilation during the BFR and Post BFR-A trial,
- significant increases in blood flow with BFR, BFR-A and BFR-R,
- significant decrease in muscle oxygenation when BFR was carried out in combination with aerobic and resistance exercise,
- the type of exercise does not affect the influence BFR training has on blood flow and muscle oxygenation
- strong correlations between blood flow and vasodilation as well as blood flow and muscle oxygenation.

2.4.1 Effects on Vasodilation

Significant increases in vasodilation were observed during the BFR trial. This corresponds to how FMD normally takes place in response to reactive hyperemia affirming the ability of BFR to induce FMD which may then be used in assessing endothelial dysfunction (Horiuchi & Okita, 2012). The brachial artery, in particular, has been useful in accomplishing this as it can independently predict cardiovascular events (Celermajer et al., 1992; Gokce et al., 2003). Moreover, aerobic exercise-induced vasodilation may be guided by the release of NO, a well-established vasodilator acting within the endothelium (Gaenzer et al., 2001). Therefore, the addition of aerobic exercise to BFR may augment the release of NO, leading to the greatest increase in vasodilation seen during BFR-A and the significant increase at the post BFR-A phase.

Alternatively, the isometric nature of the resistance exercise in the current study can decrease vasodilation as demonstrated by McGowan and colleagues (2006). This may counter the vasodilatory effects of BFR leading there to be a noticeably smaller increase in vasodilation as compared to all other testing conditions. Further research would be needed to examine the effects of vasodilation on aerobic and resistance exercise outside of BFR.

2.4.2 Effects on Total Blood Flow

Total blood flow in the brachial artery was greatest when exercise was combined with BFR. However, the type of BFR exercise seemingly did not make a difference in the change in blood flow. This is contradictory to Collier et al. (2010) who observed resistance exercise to have a greater increase in blood flow compared to aerobic exercise. This dissimilarity may, in part, be due to the presence of BFR in the current study. To further solidify this claim, studies have found that low intensity resistance and aerobic exercise with BFR showed greater increases in hemodynamic response (measured by cardiac output, stroke volume, heart rate and blood pressure) when compared to their non-BFR counterparts (Staunton et al., 2015; May et al., 2017). This indicates that the increase in blood flow in the current study may be credited to the combination of BFR and exercise and not just exercise alone.

Similar to the changes in vasodilation, the significant increase in blood flow with BFR, BFR-A and BFR-R is likely due to reactive and active hyperemia. Furthermore, the correlations found between blood flow and vasodilation as well as blood flow and muscle oxygenation point to the natural cascade of events during reactive and active hyperemia. In reactive hyperemia, the shear stress on the vessel walls initiates vasodilation, allowing for greater blood flow and, consequently, greater muscle oxygenation. In active hyperemia, the body senses a lack of oxygen in the muscles and responds with vasodilation and increased blood flow. The data may, therefore, be explained by these two sequences of events.

2.4.3 Effects on Muscle Oxygenation

Muscle oxygenation results mirrored that of blood flow further cementing their strong association (r= -0.562). The only difference observed between these two outcomes was the non-significance of the Control vs BFR difference in muscle oxygenation. A potential explanation for this could be that active hyperemia (seen with BFR-A and BFR-R) has a stronger influence on muscle oxygenation levels than reactive hyperemia alone (seen with BFR). The exercise during active hyperemia creates a hypoxic environment in the muscles which elicits a response in the blood flow creating a negative feedback loop. This explanation is also in agreement with how strong correlations between blood flow and muscle oxygenation were seen in both BFR exercise trials and not with the BFR only trial.

2.4.4 Limitations and Conclusion

Limitations to this study include the inconsistent time of day at which testing sessions took place. This could have impacted physical activity levels, food intake, and stress levels between participants. A future study should restrict the testing sessions to a 3-hour time period to control for these factors. In addition, the current study only compared BFR exercise, BFR alone and no BFR (Control). This fails to acknowledge how resistance or aerobic exercise without BFR application immediately affects vasodilation, blood flow and muscle oxygenation levels. With the addition of an "exercise only" testing condition, examining the changes that BFR elicits when added to exercise would be facilitated.

In conclusion, this study is novel in that it is the first to examine the immediate effects of BFR with and without exercise. Within a minute of BFR application, it observed significant increases in vasodilation and blood flow along with significant decreases in muscle oxygenation when BFR was applied in this healthy population. Furthermore, results showed no significant differences when comparing BFR-A with BFR-R for blood flow and muscle oxygenation suggesting that the type of exercise does not play a role in affecting these two outcomes. Finally, strong associations were seen when comparing blood flow with muscle oxygenation and blood flow with vasodilation in the BFR testing condition. These results provide insight into the immediate effects of reactive and active hyperemia and are only the first step in understanding the complete influence of BFR on the body.

2.4.5 Acknowledgements

We would like to acknowledge and thank our young adult participants who made the time to come in and be tested for this study.

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2.6 Appendix

	N	Age *Mean (SD)*
Male	14	25.36 (3.10)
Female	16	23.94 (4.19)
Total	30	24.60 (3.73)

Table 1. Participant characteristics

Inclusion Criteria	• Between 18 and 35 years of age • Male or female • Functional left arm • English or French speaking
Exclusion Criteria	• Under 18 years of age • Over 35 years of age • Presence of cardiovascular disease • Recent injuries on the left arm that cause pain or difficulty moving • Pregnant

Table 2. Participant inclusion and exclusion criteria

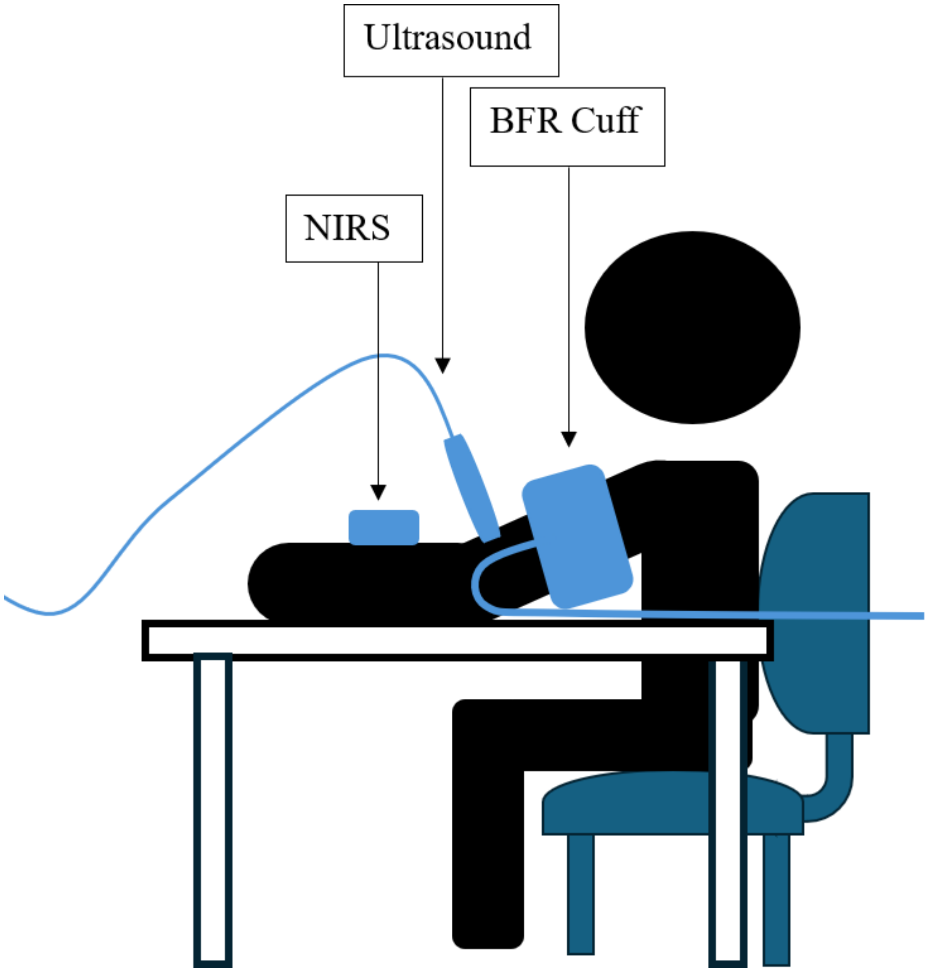


Figure 1. Set up of participant during testing session

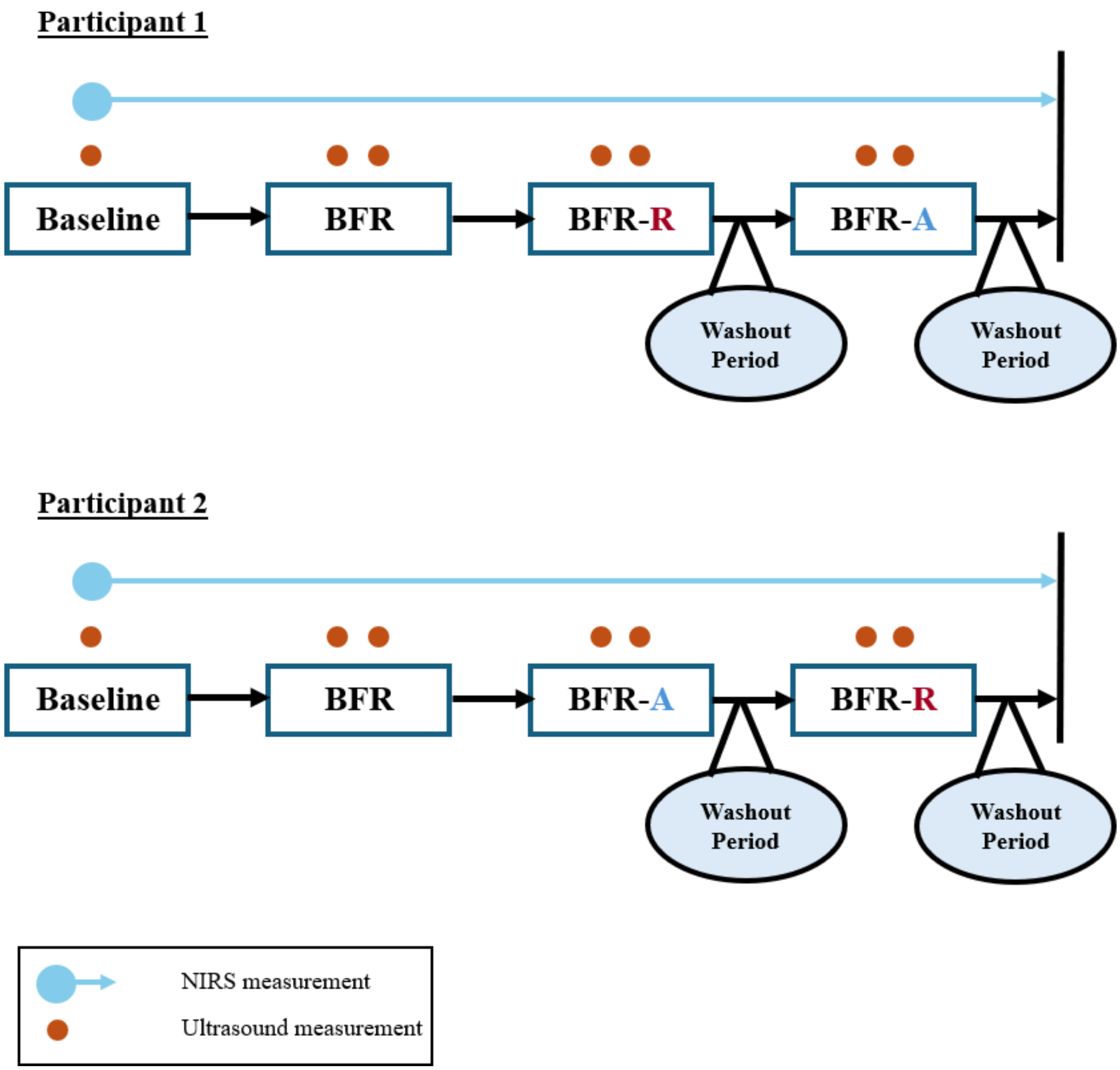
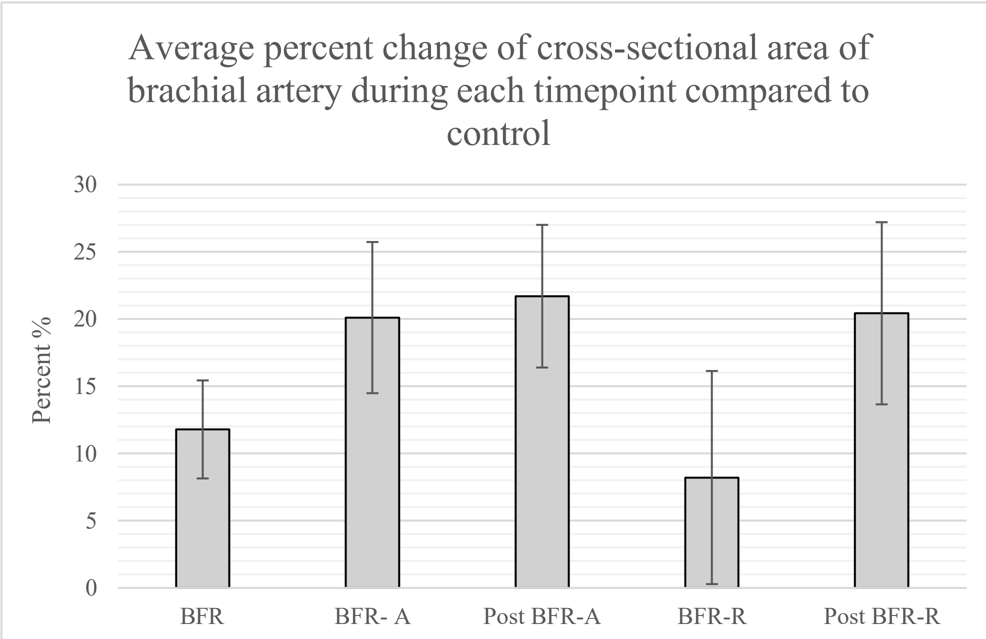
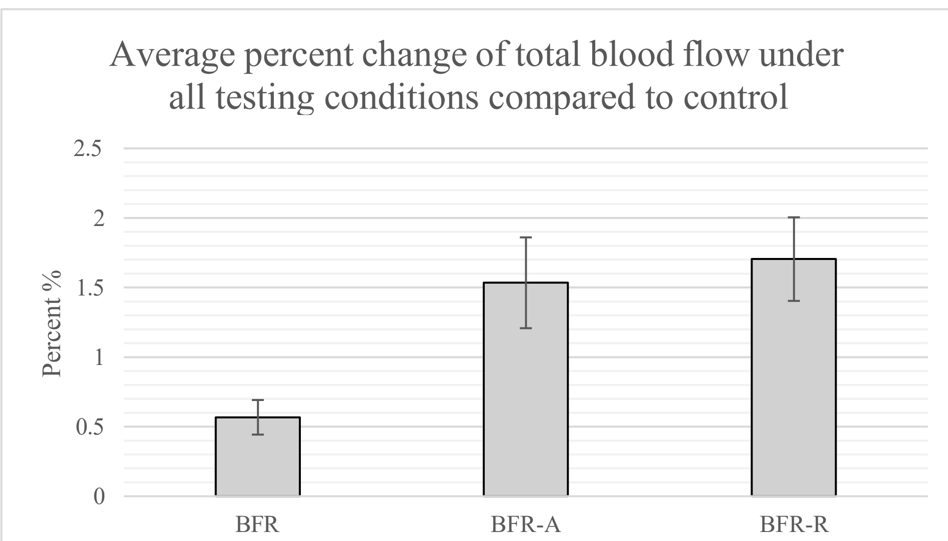


Figure 2. An example of the study procedure between 2 participants



<u>Figure 3. Mean percent change of brachial artery area between each testing condition and control. Standard error represented through error bars.</u>



<u>Figure 4. Mean percent change of total blood flow in the brachial artery between each testing condition and control. Standard error represented through error bars.</u>

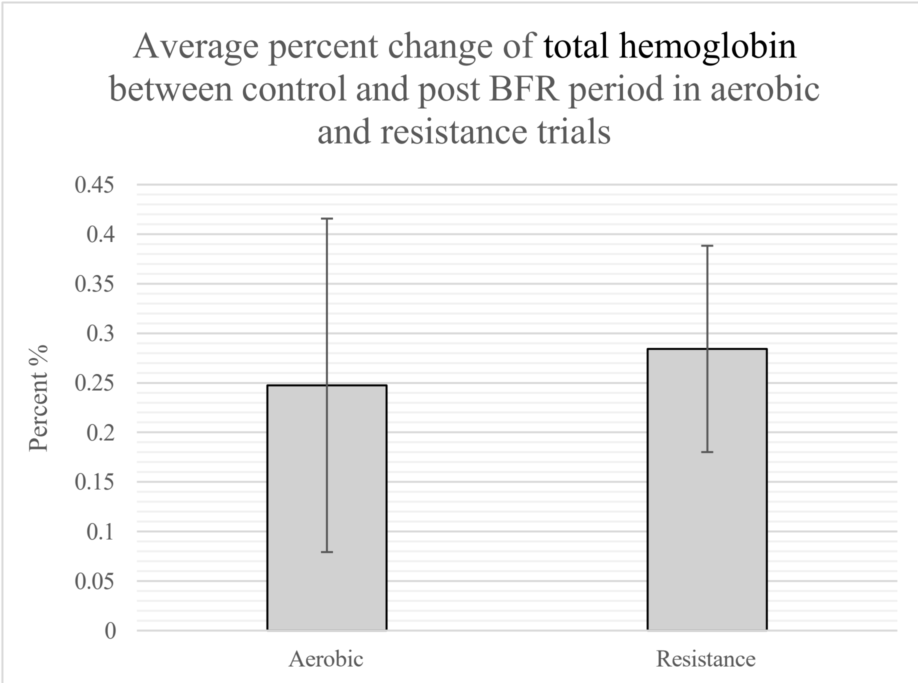


Figure 5. Mean percent change of blood flow after BFR exercise trials compared to control trial

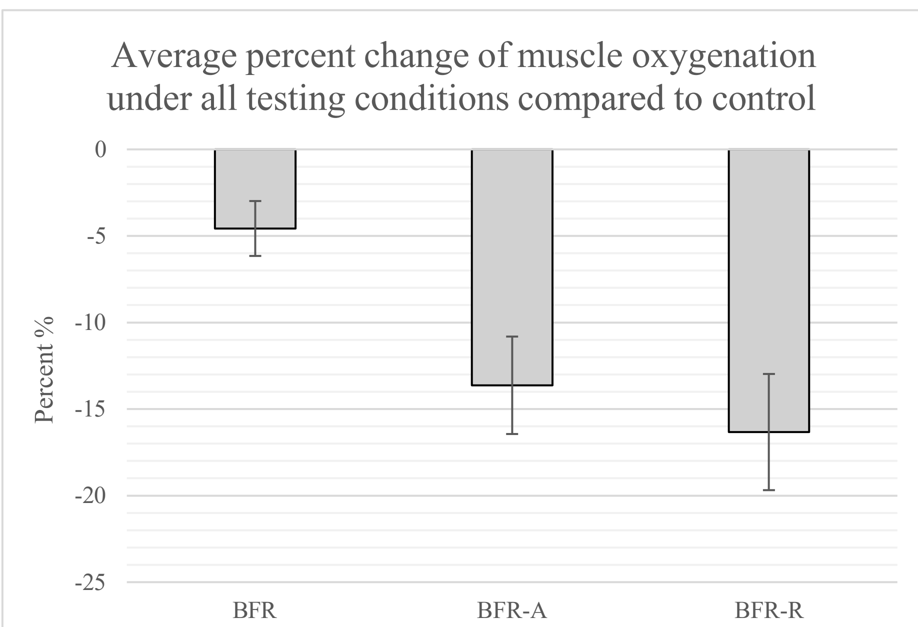


Figure 6. Mean percent change of muscle oxygenation in the forearm muscles between each testing condition and control. Standard error represented through error bars.

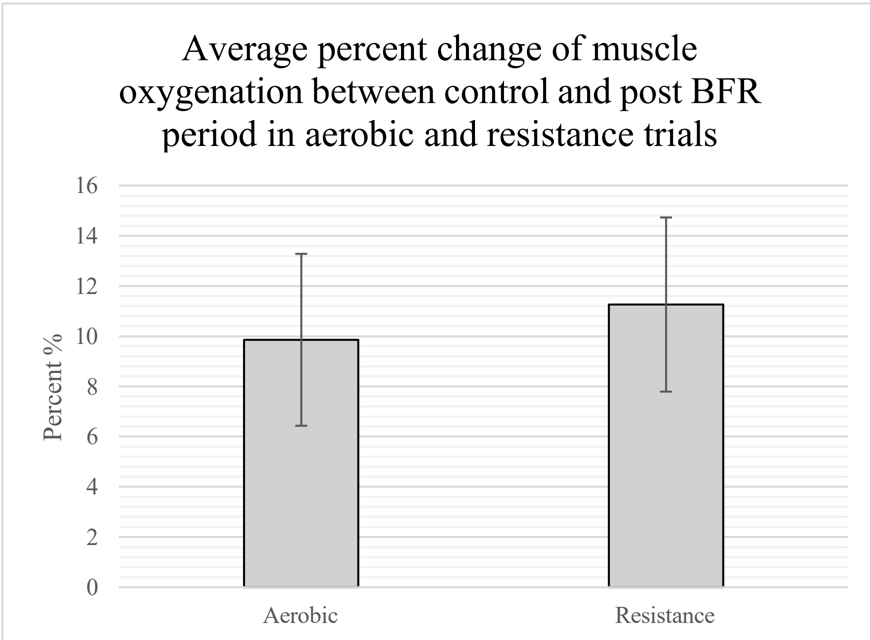


Figure 7. Mean percent change of muscle oxygenation after BFR exercise trials compared to control trial

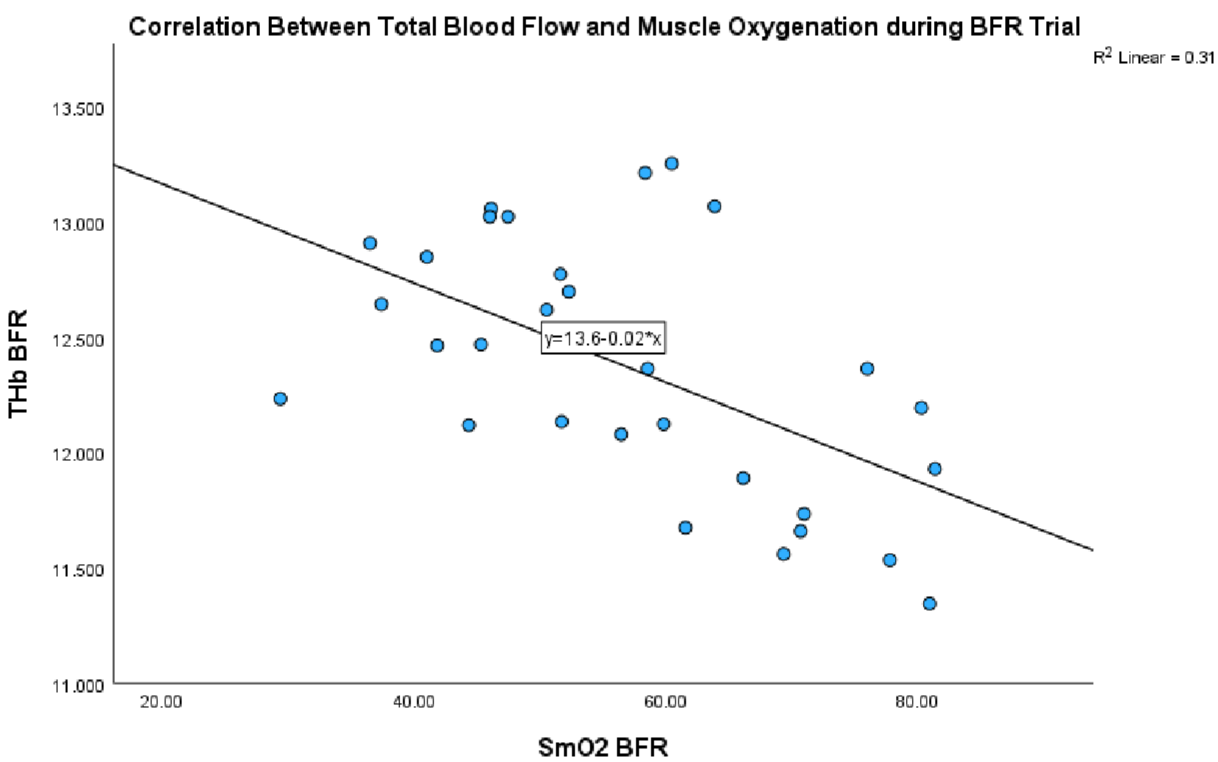


Figure 8. Correlation between blood flow and muscle oxygenation during BFR trial

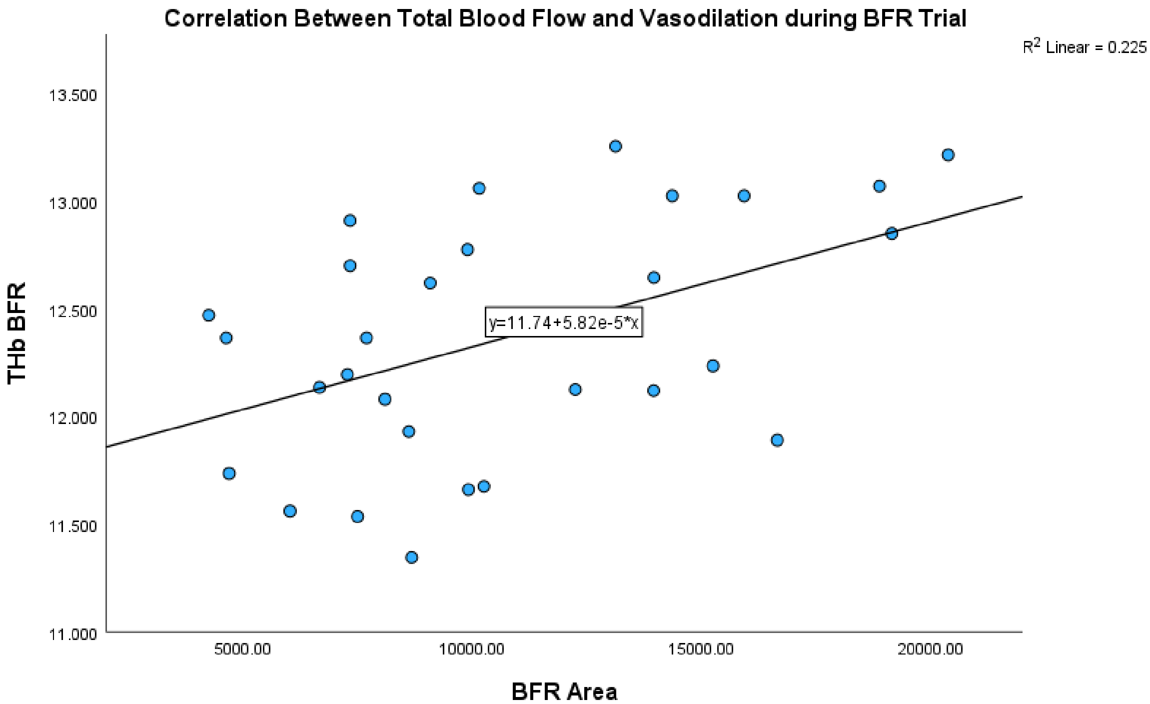


Figure 9. Correlation between blood flow and vasodilation during the BFR trial

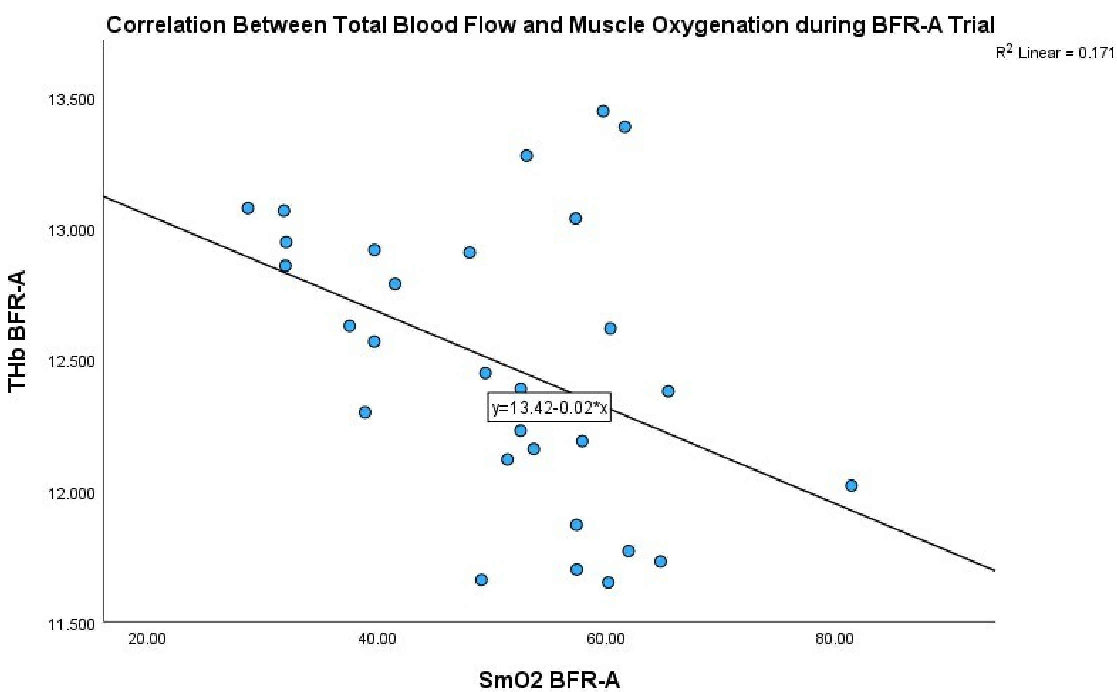


Figure 10. Correlation between blood flow and muscle oxygenation during BFR-A trial

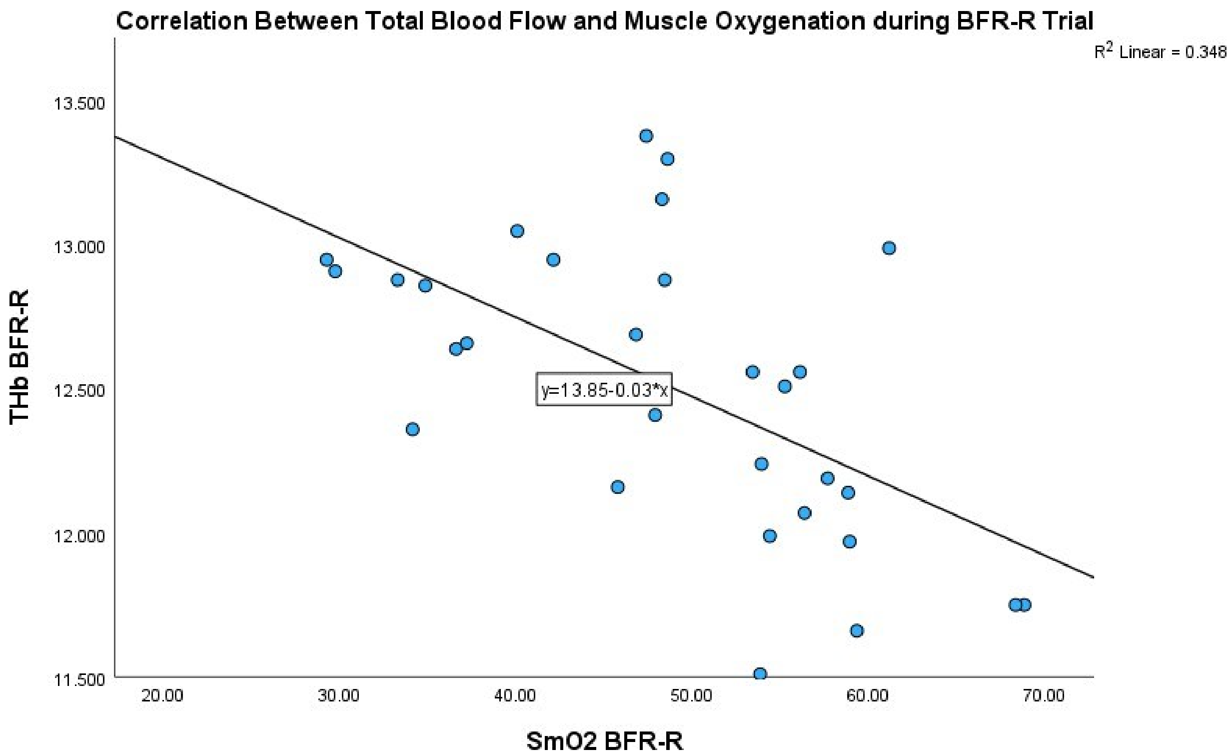


Figure 11. Correlation between blood flow and muscle oxygenation during BFR-R trial

CHAPTER 3. CONCLUSION AND FUTURE DIRECTIONS

This study's aim was to gain insight into the immediate effects of BFR on vasodilation, blood flow, and muscle oxygenation in a young and healthy population. It demonstrated that there is much that happens within as little as one minute of BFR application. Reactive and active hyperemia play essential roles in bringing out these changes and the addition of exercise to BFR further intensifies effects on the outcomes.

This study was the first step in discovering the immediate effects of BFR. Many avenues remain open for future research:

1. Carry out this same study in different populations. This can be done with older adults, patients with cardiovascular disease, smokers, runners, etc.
2. Study the effects of vasodilation, blood flow and muscle oxygenation under different time points. For example, one may look at these outcomes with 30 minutes of BFR application during exercise and how they are affected at each minute up to 5 minutes post BFR.
3. Explore the immediate effects of rest incorporated with BFR on these same outcomes. This may be carried out with a short BFR exercise session and subsequently allowing rest periods with BFR still applied to the limb.
4. Study the immediate effects of BFR on other outcomes such as NO concentration, cardiac output, heart rate and blood pressure.

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