Effects of Volume Set-Equated High Intensity Resistance Training Programs with and without Blood Flow Restriction on Morphological and Physiological Adaptations

RATANYOO LONGRAK

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR DOCTOR DEGREE OF PHILOSOPHY
IN EXERCISE AND SPORT SCIENCE
FACULTY OF SPORT SCIENCE
BURAPHA UNIVERSITY
2024

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รตัญญู หลงรัก

ดุษฎีนิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปรัชญาดุษฎีบัณฑิต
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The Dissertation of Ratanyoo Longrak has been approved by the examining committee to be partial fulfillment of the requirements for the Doctor Degree of Philosophy in Exercise and Sport Science of Burapha University

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RATANYOO LONGRAK : EFFECTS OF VOLUME SET-EQUATED HIGH INTENSITY RESISTANCE TRAINING PROGRAMS WITH AND WITHOUT BLOOD FLOW RESTRICTION ON MORPHOLOGICAL AND PHYSIOLOGICAL ADAPTATIONS. ADVISORY COMMITTEE: WIRAT SONCHAN, Ph.D. KAWIYA SINTARA, Ph.D. PARINYA RUENGTIP, Ph.D. 2024.

Background: Resistance training program design was crucial for eliciting optimal adaptations from resistance training. This study aimed to investigate and compare morphological and physiological adaptations from two high intensity resistance training programs. *Methods*: Twenty untrained male participants were recruited and assigned to traditional high intensity resistance training program (TRAD) or high intensity combined with low intensity resistance training with blood flow restriction program (LLpBFR). Both programs were periodized to equate volume sets. Muscle cross-sectional area (MCSA) and muscle thickness (MT) of biceps brachii (BB) and vastus lateralis (VL), muscle architectures of VL, maximum strength metrics, ankle-brachial index (ABI), and perception of effort (OMNI-RES) were measured at Pre- and Post-intervention. *Results*: The significant increases were observed in both groups (all $p<0.05$) in MCSA and MT of BB (TRAD: □5-12.1% and □5.1-25.3%; LLpBFR: □7.9-16.9% and □6.4-24.5%, respectively) and VL (TRAD: □8.7-14% and □6.5-15.2%; LLpBFR: □9.1-12.7% and □13.4-24.8%, respectively). Moreover, fascicle length significantly increased in both groups (TRAD: □16.9% and LLpBFR: □15.8%, all $p<0.05$). Furthermore, maximum strength metrics significantly increased in both groups to similar extent ($p<0.05$), yet OMNI-RES scores were significantly lower in LLpBFR in the first two weeks of programs ($p<0.05$). Besides, both groups had their ABI score unchanged from Pre- to Post-intervention ($p>0.05$), with no difference between group. *Conclusion*: Both TRAD and LLpBFR were effective for inducing positive morphological adaptations. However, the results suggested that practitioners did not necessarily need to maintain high intensity in every set throughout the program to achieve maximum strength gains. Consequently, LLpBFR offered additional benefits, both physiologically by potentially reducing muscle damage and joint stress, and psychologically by potentially lowering the perception of effort, particularly in the early weeks of training.

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I am incredibly grateful to my family and good friends and ex-friends for their support throughout this journey. Pursuing a Ph.D. has been a transformative experience, significantly enhancing my critical thinking and scholarly abilities. Additionally, I have developed a profound appreciation for the field of statistics!

Achieving this milestone has been a dream come true. Six years ago, in the acknowledgment section of my Master's thesis, I wrote, "this is not my last." Today, I am proud to say that I have fulfilled that promise. I know my mother will be proud, and I look forward to sharing this accomplishment with her and my supportive community. Thank you, Mom, for everything.

Ratanyoo Longrak

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CHAPTER 1
INTRODUCTION

Background

The human body contains hundreds of thousands of muscle fibers, which are highly adaptable and can increase in size and strength in response to training (Vikne et al., 2020). Resistance training is the effective method to increase muscle mass, strength, and fitness. The intensity of external load recommended for inducing strength and hypertrophy is typically based on the strength continuum of an individual, referred as one-repetition maximum (1RM) (Fisher et al., 2020). For muscle hypertrophy, the American College of Sports Medicine recommends that novice and intermediate individuals train at 70-85%1RM, performing 1 to 3 sets of 8-12 repetitions per exercise with 1-2 minutes of rest between sets. Additionally, for muscular strength, novice individuals are advised to train the entire body 2-3 times per week at 60-70%1RM for 8-12 repetitions, performing 1-3 sets per exercise, with a gradual increase in load and 2-3 minutes of rest between sets (Ratamess et al., 2009).

However, the current body of literature consistently demonstrates that both low and highintensity training are equally effective in promoting muscle hypertrophy. For example, Fink et al. (2016) reported significant increases in muscle cross-sectional area from both high (80%1RM) and low intensity (30%1RM) training, with no significant difference between groups. Similarly, Lasevicius et al. (2019) demonstrated that both high and low intensity training produced comparable increases in quadriceps cross-sectional area (8.1% vs. 7.8%) over 8 weeks. Recently, a meta-analysis by Schoenfeld et al. (2017), analyzing 21 studies, concluded that muscle hypertrophy can be achieved across a wide range of loading intensities. In this analysis, low intensity was defined as training with a load of less than or equal to 60%1RM. However, it is important to note that the upper limit of this defined low intensity can still be quite challenging for certain groups, such as individuals with no experience or recovering from injury or those with skeletal disorders. Therefore, it is likely that high intensity resistance training (>70%1RM) is not always necessary for hypertrophy.Furthermore, Lixandrao et al. (2018) conducted another meta-analysis, comparing high and low intensity training, where low intensity was defined as less than or equal to 50%1RM. This analysis included 10 studies with a combined sample size of 368 participants and found that muscle mass gains were comparable between high and low intensity training. It is noteworthy that in all 10 studies, low intensity training was conducted at 10-30%1RM, which contrasts with the American College of Sports Medicine's recommendation of 70-100%1RM for muscle hypertrophy. These findings suggest that muscle hypertrophy may not be dependent on load, and other factors should be considered.

This concept is reinforced by multiple studies. Lasevicius et al. (2018) demonstrated that training at various intensities, from 20%, 40%, 60%, and 80%1RM over 12 weeks, can all successfully induce muscle hypertrophy. Similarly, Schoenfeld et al. (2021) revisited the intensity required for hypertrophy, challenging the traditional "Strength-Endurance Continuum." This continuum posits that high-intensity training (80-100%1RM) enhances maximal strength, moderate-intensity training (60-80%1RM) induces hypertrophy, and low-intensity training (<60%1RM) improves muscular endurance. Emerging evidence suggests that a broad range of loads, starting from 30%1RM, can achieve significant muscle hypertrophy, irrespective of age or training status (Schoenfeld et al., 2021). Notably, an unusual study by Counts et al. (2016) found that even training with no load (0%1RM), by merely contracting the elbow flexors, resulted in substantial hypertrophy in the biceps. Therefore, a specific "hypertrophy zone" does not exist. Additionally, Schoenfeld (2013) proposed that factors such as metabolic stress, which causes cell swelling and systemic hormonal elevations, may enhance muscle hypertrophy when low-intensity training is utilized.

From mechanism perspectives, two primary stimuli play the main role in inducing hypertrophic adaptation: mechanical tension and metabolic stress (Schoenfeld, 2010). Wackerhage et al. (2018) assert that mechanical tension, typically achieved through high intensity training, is sufficient to induce skeletal muscle hypertrophy via increasing signaling pathways that increases muscle protein synthesis. Metabolic stress, on the other hand, contributes to hypertrophy, albeit to a lesser extent. From molecular standpoint, muscle mass increases due to a positive protein balance, which occurs when protein synthesis exceeds protein degradation (Burd et al., 2012). Each bout of resistance exercise leads to an acute increase in protein synthesis, cumulatively promoting muscle growth (Figueiredo, 2019).

Specifically, the primary mechanism by which mechanical tension induces skeletal muscle hypertrophy is through mechano-transduction (Burkholder, 2007). Mechano-transduction involves a cellular electro-biochemical cascade that converts mechanical stimuli, such as the deformation of individual myofibers, into signals that enhance muscle protein synthesis (Burkholder, 2007; Hamilton et al., 2009; Yamada et al., 2011). Initially, it was believed that larger loads had a greater impact on muscle protein synthesis compared to smaller loads. For example, Kumar et al. (2009) found that lifting at 20%1RM for a total of 81 repetitions resulted in lower muscle protein synthesis than lifting at 60%1RM for 24 repetitions and at 90%1RM for 18 repetitions in both young and older adults. However, later research indicated that the low intensity training in the study did not involve lifting to failure, which might have influenced the results. To investigate this, a study compared training at 30%1RM and 90%1RM, both to failure, and found that both intensities stimulated muscle protein synthesis to the same extent (Burd et al., 2010). Consequently, it was suggested that maximizing muscle protein synthesis is not solely dependent on mechanical-tension-induced mechano-transduction. Other factors, such as metabolic stress, also play a significant role, especially in low-intensity training to failure (Schoenfeld, 2013).

Over the past several decades, various mechanisms have been proposed to explain how metabolic stress stimulates skeletal muscle hypertrophy. These mechanisms include increased muscle protein synthesis (Burd et al., 2010; Hwang & Willoughby, 2019), the effects of ischemic conditions on working muscles (Manini & Clark, 2008), elevated motor unit recruitment (Wernbom et al., 2008; Schoenfeld, 2013), cell swelling (Rolnick & Schoenfeld, 2020; Schoenfeld et al., 2014), enhanced metabolite production (Schoenfeld, 2013; Rolnick & Schoenfeld, 2020), increased hormonal release (Thurston & Burr, 2017; Schoenfeld, 2013), and the up-regulation of muscle satellite cell activity (Pearson & Hussain, 2014; Jessee et al., 2018). Due to the current limited understanding, it is difficult to definitively exclude any of these mechanisms as contributors to muscle hypertrophy in response to metabolic stress. Existing literature often alternately supports and questions these mechanisms, leaving all as possible contributors to muscle hypertrophy.

For muscle strength development, several chronic adaptations contribute to enhancing maximum strength. Morphologically, an increase in muscle size or hypertrophy plays a significant role in increasing maximum strength (Suchomel et al., 2018). Numerous studies have shown that hypertrophy training leads to significant increases in muscle strength alongside muscle growth. For instance, Barbalho et al. (2020) found that hip thrust and squat exercises effectively increased both the thickness of the gluteus and quadriceps muscles, and the 1RM strength of hip thrusts and squats after 12 weeks of training. This increase in strength is likely due to hypertrophy-induced growth in type II fiber cross-sectional area, which enhances the muscle's capacity to generate force and power (MacDougall & Sale, 2014).

Neurologically, resistance training can induces several neural adaptations that chronically impact muscle strength, including increased motor unit recruitment, firing frequency, and synchronization (Suchomel et al., 2018). A recent meta-analysis provides strong evidence that both low intensity (□60%1RM) and high intensity (□65%1RM) can significantly increase muscle size and strength from baseline. However, to maximize muscle strength, high intensity resistance training shows a trend of superiority over low intensity training (Schoenfeld et al., 2016). In agreement with a meta-analysis of Lixandrao et al. (2018) who found that although low intensity training with special technique such as blood flow restriction can induce muscle hypertrophy, the increase in maximum strength is still suboptimal compared to high intensity training. This suggests that while muscle hypertrophy can be achieved across various loading ranges, maximizing strength development requires incorporating high intensity training into training programs.

In practice, to induce a hypertrophic response from low intensity training, two critical conditions should be met. First, the working muscle must be trained to momentary muscular failure, as consistently demonstrated in the literature (Mitchell et al., 2012; Ogasawara et al., 2013; Schoenfeld, 2013; Lasevicius et al., 2019). Studies have shown that low intensity training that does not reach muscular failure often results in suboptimal hypertrophic outcomes. For instance, Burd et al. (2010) compared low intensity training at 30%1RM with and without reaching failure. They found that significant increases in muscle protein synthesis were only observed in the group that trained to failure. Conversely, the group that ceased before reaching failure did not achieve a maximal muscle protein synthesis response post-exercise.

Similarly, Takarada et al. (2000) observed that electromyography levels during low intensity training at 50%1RM were about 40% lower than those during high intensity training at 80%1RM. However, when the low intensity protocol was taken to failure, EMG levels were comparable to high intensity training. This finding was corroborated by Ikezoe et al. (2017), who compared low intensity, high repetition training (30%1RM, 12 sets of 8 repetitions) to high intensity, low repetition training (80%1RM, 3 sets of 8 repetitions). After 8 weeks of training, the high intensity group saw a 20.4% increase in quadriceps rectus femoris muscle thickness, while the low intensity group only experienced an 11.3% increase, despite performing nearly double the total training volume (6069 N vs. 3084 N per day). This contradicts the common dose-response relationship, which suggests that higher volumes equate to greater muscle hypertrophy (Schoenfeld et al., 2017). It is possible that that the higher volumes without reaching failure were insufficient for meaningful hypertrophy (Baz-Valle et al., 2018). Furthermore, Lasevicius et al. (2019) found that benefits of training to failure were significant only in the low intensity group, while high intensity training to failure did not offer additional hypertrophic advantages. This indicates that to attain optimal hypertrophic results with low-intensity RT, the muscle must be trained to failure.

The second condition for enhancing hypertrophic outcomes with low intensity training is the utilization of the blood flow restriction (BFR) which has gained significant attention among researchers (Manini & Clark, 2009). BFR training involves the intentional partial restriction of arterial inflow and complete restriction of venous outflow in the targeted muscle during exercise (Scott et al., 2015). This is typically achieved using pressurized cuffs or elastic wraps applied to the proximal regions of the limbs (Patterson et al., 2019; Korkmaz et al., 2020; Wilk et al., 2020). A meta-analysis by Centner et al. (2019) comparing found that, consistent across 11 studies with a total of 238 subjects, low intensity BFR training resulted in muscle mass increases comparable to those of high intensity training. Additionally, low intensity BFR training reduces mechanical stress on bones, joints, and muscles (Scott, 2014), making it beneficial for recovery periods and populations such as older adults or individuals with musculoskeletal injuries. However, the traditional BFR method can be costly, limiting its accessibility. An alternative, more cost-effective approach involves using elastic knee or elbow wraps, known as practical BFR (Loenneke et al., 2009; Wilson et al., 2013; Luebbers et al., 2014; Scott et al., 2017). While practical BFR aims to provide similar stimuli as standard pressurized cuffs, the scientific evidence supporting its efficacy remains limited, necessitating further research.

BFR is working on the hypothesis that metabolic stress promotes muscle hypertrophy by facilitating training at low intensities, typically ranging from 20-50%1RM (Wernbom & Aagaard, 2019), and sometimes as low as 10% 1RM (Thiebaud et al., 2013), which is contrary to the hypertrophy guidelines of the American College of Sports Medicine. BFR training is theorized to accelerate metabolite accumulation, thereby inducing hypertrophy without high mechanical loads (Schoenfeld, 2013; Ozaki et al., 2015; Wackerhage et al., 2018). The growing body of literature supports the effectiveness of low-intensity BFR training for promoting muscle hypertrophy (Takarada et al., 2000; Yamanaka et al., 2012; Luebbers et al., 2014; Scott et al., 2017; Bjornsen et al., 2019; Centner et al., 2019). These studies indicate that RT with loads ranging from 20-50%1RM can optimize muscle hypertrophy to a significant degree.

Practically, while both low and high intensity resistance training have been shown to promote skeletal muscle hypertrophy, high-intensity RT also has significant concern for vascular function and joint stress. During intense muscle contractions with high external loads, there is an increase in systemic vascular resistance, leading to elevated systolic and diastolic blood pressure. This phenomenon, known as vasoconstriction, helps to redistribute blood to the working muscles but also increases the workload on the heart, potentially resulting in arterial hypertension (MacDougall & Sale, 2014). Physiologically, arterial hypertension, whether acute or chronic, has been associated with arterial dysfunction and conditions such as peripheral artery disease (Dharmashankar & Widlansky, 2010). For example, a study by Jurva et al. (2006) found that a single session of heavy leg press exercises led to a 5% decrease in arterial dilation function for up to one hour after exercise in healthy subjects. This suggests that the acute hypertensive response to high-intensity exercise can impair vascular function, even in individuals without preexisting vascular issues.

Moreover, high intensity resistance training can exacerbate vascular issues in individuals with hypertension. Panza et al. (1990) demonstrated that hypertensive patients exhibited impaired vascular dilation, evidenced by reduced forearm blood flow in response to acetylcholine, suggesting that such training may further compromise vascular function in those with elevated blood pressure. Additionally, the sustained muscle contractions against heavy loads during high-intensity training can lead to prolonged elevated pressure, potentially causing a decline in vascular dilation over time (Fuchs & Whelton, 2020). Although high intensity training is effective for strength and hypertrophy, it presents significant risks to vascular health, particularly concerning arterial pressure and function, which requires careful consideration for individuals with or at risk of hypertension. This concern is further supported by Atkinson et al. (2015), who found that the use of alpha-1 adrenoreceptor blockers preserved vascular dilation post-exercise compared to a placebo. Physiologically, repeated dynamic muscle contractions against heavy loads increase sympathetic nerve activity, leading to norepinephrine release and subsequent vasoconstriction via alpha receptors (MacDougall & Sale, 2014). By blocking these receptors, the medication limits vasoconstriction, thereby reducing systemic vascular resistance and lowering blood pressure during exercise.

Looking from vascular function perspective, high and low intensity resistance training with BFR may have distinct effects on vascular function. Blears et al. (2021) noted that low intensity training involves low external loads, high repetitions, prolonged time under tension per set, and lower muscle force per contraction, similar to aerobic exercise. Similarly, Lekavich et al. (2021) observed that aerobic activities, such as cycling and climbing, which involve continuous muscle contractions against low resistance, offer greater benefits for peripheral vascular structure by showing that after 6 months of aerobic training, brachial artery post-hyperemia peak diameter significantly increased. In contrast, high intensity resistance training at 70-85%1RM has showed to decrease the peak diameter after intervention. Additionally, Mang et al. (2022) proposed that resistance training with prolonged time under tension (>60seconds per set) and high number of repetition (>20repetition) could stimulate the expression of peroxisome proliferator-activated receptor gamma coactivator 1-alpha or PGC-1alpha. Physiologically, This PGC-1alpha can up-regulate vascular endothelial growth factor activities, promoting new capillary formation, potentially improving hemodynamic function long-term, and improving aerobic capacity of practitioners. However, further research is warranted to confirm the benefits of low intensity resistance training on vascular function.

Last but not least, high intensity resistance training is often associated with a high perception of effort, which can influence both performance and adherence to training programs. A study by Borg (1998) introduced the Rate of Perceived Exertion (RPE) scale, which has been widely used to quantify how hard an individual feels they are working during exercise. Subsequent studies, such as those by Gearhart et al. (2002), have demonstrated that higher resistance loads correspond with higher RPE scores, indicating that as intensity increases, so does the subjective experience of effort. This elevated perception of effort can be a limiting factor, particularly for individuals who are less trained or have a lower tolerance for discomfort, potentially impacting the long-term sustainability and effectiveness of high-intensity resistance training programs. Therefore, while this type of training is effective for achieving strength and hypertrophy, its high perception of effort must be carefully managed to ensure adherence and minimize the risk of overtraining or burnout.

Today, the OMNI-Resistance Exercise Scale (OMNI-RES) is commonly used to assess perceived exertion during resistance training. Developed by Robertson et al. (2003), the OMNI-RES scale is a validated tool that provides a more specific measure of perceived exertion tailored to resistance exercises. Unlike the traditional Borg RPE scale, which was initially designed for aerobic activities, the OMNI-RES scale includes visual cues and descriptors that are directly relevant to resistance training, making it more intuitive and user-friendly for individuals engaging in weightlifting or strength training. Studies have shown that the OMNI-RES scale effectively correlates with physiological markers such as heart rate and blood lactate levels, reinforcing its reliability and accuracy in capturing the intensity of resistance training sessions (Lagally et al., 2004). As a result, the OMNI-RES scale has become a valuable tool for both practitioners and researchers, helping to standardize the measurement of effort across different exercises and intensities, and ultimately enhancing the safety and effectiveness of resistance training programs.

Statement of the Problem

Despite the growing body of literature examining the similarities and differences between high intensity resistance training and low intensity resistance training with blood flow restriction (BFR), it remains unclear whether combining these two modalities could produce additive or synergistic benefits for muscle hypertrophy, strength, and vascular function compared to high intensity resistance training alone. The metabolic stress and aerobic demands associated with the prolonged time under tension and high repetitions characteristic of low intensity training with BFR suggest unique advantages that warrant further exploration. However, most research has primarily compared low intensity resistance training with BFR against high intensity resistance training in isolation, rather than investigating the potential benefits of combining these approaches. Consequently, there is a critical need for studies examining the combined effects of these training regimes to determine whether they offer superior outcomes in hypertrophy, strength, and overall vascular health. Additionally, considering that practitioners often struggle to sustain high intensity sets throughout training sessions due to physical or mental fatigue and the increased risk of injury associated with high intensity training, this study aims to address these gaps by evaluating whether a combined protocol can reduce the perception of effort. Furthermore, this combined protocol will test the hypothesis proposed by previous studies that incorporating both high intensity and low intensity sets is necessary to maximize hypertrophy and strength outcomes (Helms et al., 2014).

Therefore, the purpose of this current study is to investigate and compare the chronic morphological and physiological adaptations resulting from two volume set-equated training programs: *Traditional high intensity resistance training* (TRAD) and *High intensity resistance training combined with low intensity resistance training with practical blood flow restriction* (LLpBFR).

Research Questions

1) Can combining high intensity and low intensity resistance training with blood flow restriction serve as an effective alternative to high intensity resistance training for chronic morphological and physiological adaptations?

Research Objectives

1) To compare changes in the muscle thickness and muscle cross-sectional area of the vastus lateralis and biceps brachii from pre-test to post-test within and between groups.
2) To compare changes in the architecture of the vastus lateralis from pre-test to post-test within and between groups.
3) To compare changes in dynamic strength and isometric strength from pre-test to post-test within and between groups.
4) To compare changes in the ankle brachial index score from pre-test to post-test within and between groups.

Research Hypotheses

1) Vastus lateralis and Biceps brachii thickness and cross-sectional area will significantly increase in both training groups.
2) Muscle architectural adaptations will improve in similar manner between training groups.
3) TRAD will affect vascular function, as measured by the ankle-brachial index, while chronic LLpBFR training will improve or maintain ankle-brachial index.

Variables of Interest

1) Independent variables
    a. TRAD = *Traditional high intensity resistance training*
    b. LLpBFR = *High intensity resistance training combined with low intensity resistance training with practical blood flow restriction*
2) Dependent variables

a. Morphological adaptations
    i. Muscle thickness of Vastus lateralis (cm)
    ii. Muscle thickness of Biceps Brachii (cm)
    iii. Muscle cross-sectional area of Vastus lateralis (mm^2)
    iv. Muscle cross-sectional area of Biceps Brachii (mm^2)
    v. Vastus lateralis fascicle angle (degree)
    vi. Vastus lateralis fascicle length (mm)
    vii. Vastus lateralis fascia thickness (cm)

b. Physiological adaptations
    i. Isometric strength (N)
    ii. Dynamic strength (kg/lbs)
    iii. Strength to bodyweight ratio (N/kg)
    iv. Ankle-brachial index (ratio)

Scope of the Study

1) The significant problems of this current study are focusing on investigating and comparing the morphological and physiological adaptations between two training protocols: TRAD and LLpBFR, both within and between the groups
2) This study is the quantitative research: a single-blinded experimental design.
3) The participants are young healthy untrained active males.
4) The location where the data is collected and specific resistance training program is controlled is at the training room at Faculty of Sport Science, Burapha University.
5) The duration of training and data collection is 6 weeks and data analyses are processed afterwards around 2-3 weeks.

Benefits of the study

The outcomes of this study offer valuable insights into a potential alternative to traditional high intensity resistance training. The findings contribute to the expanding body of research on muscle hypertrophy and strength gains, providing practical applications for fitness professionals. Given if results can be achieved by not need to train with high intensity all the time, finding effective alternatives is crucial. Additionally, this study enhances the understanding of chronic vascular adaptations linked to different training protocols. Finally, the results may also appeal to sport scientists interested in exploring blood flow restriction techniques and their potential to promote muscle hypertrophy as a viable alternative to traditional high intensity resistance training.

Methodological framework

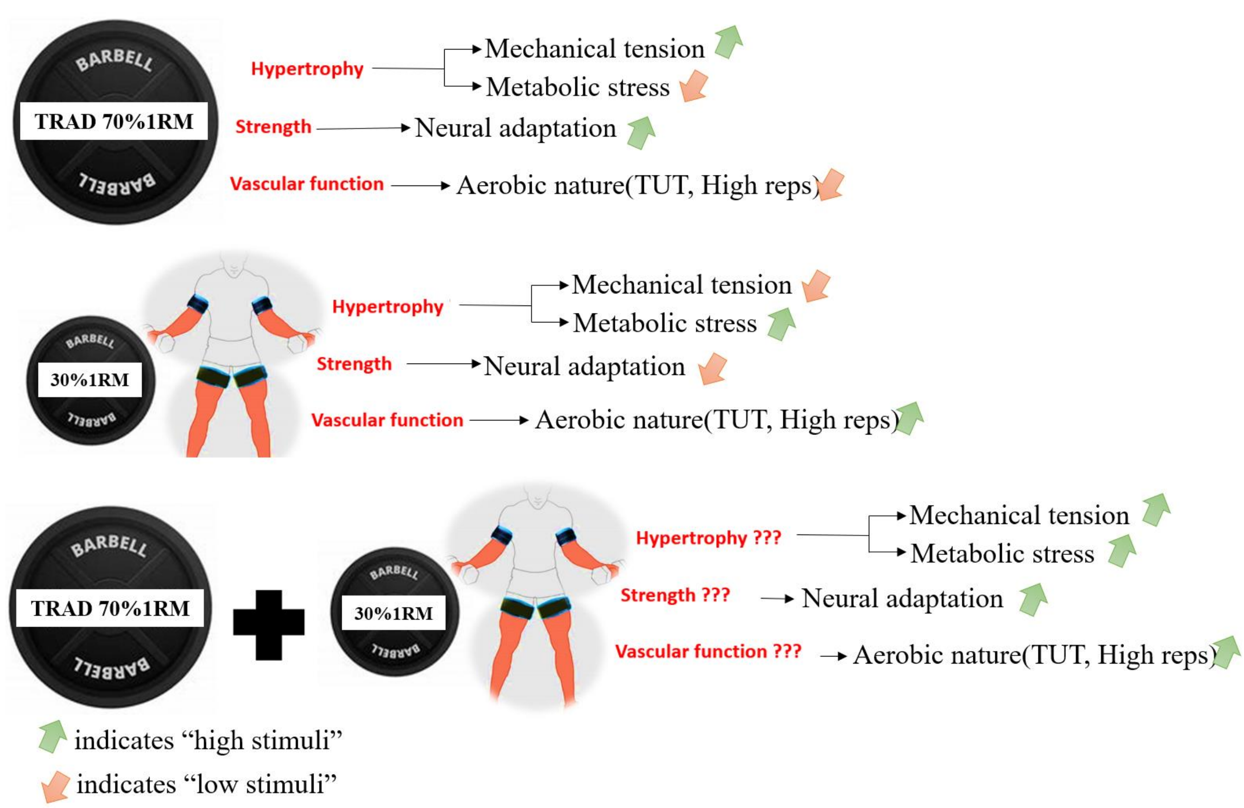


Figure 1. Methodological framework

Definition of Terms

1) TRAD = *Traditional high intensity resistance training* is a training program that adheres to the standard recommendations set by the American College of Sports Medicine, with the aim of promoting hypertrophy and strength. The intensity of training in TRAD in this study is set at 70% 1RM.

2) LLpBFR = *High intensity resistance training combined with low intensity resistance training with practical blood flow restriction* is a combined resistance training program that halves the volume for high intensity, 70%1RM, sets and low intensity, 30%1RM, sets with practical blood flow restriction. The program starts with sets of high intensity sets first, followed by low intensity sets.
3) Muscle thickness = Chronic adaptation as a result of 6 weeks resistance training, resulting in increased muscle thickness of vastus lateralis and biceps brachii.
4) Muscle cross-sectional area = Chronic adaptation as a result of 6 weeks resistance training, resulting in increased muscle cross-sectional area of vastus lateralis and biceps brachii.
5) Fascicle angle = The angle between the fascicle and the deep aponeurosis, measured in degrees, measured from proximal vastus lateralis muscle.
6) Fascicle length = The length of the fascicular path spanning from the superficial to the deep aponeuroses, as observed on ultrasound imaging, measured from proximal vastus lateralis muscle.
7) Fascia thickness = The thickness of the fascia surrounding the muscle, measured from proximal vastus lateralis muscle.
8) Isometric strength = The ability of a muscle group to generate maximum force against an immovable resistance, in a static contraction, without changing the length of the muscle. In this study, it refers to 60 degree of knee extension and 90 degree of elbow flexion.
9) Dynamic strength = The ability of a muscle group to produce force while in motion. In this study, it refers to 1 repetition maximum testing in knee extension and preacher curl exercises.
10) Chronic vascular function = In this study, vascular function refers to the measurement of Ankle-Brachii Index (ABI) for testing for risk of peripheral artery disease.

CHAPTER 2

LITERATURE REIVEWS

In this chapter, the researcher conducted a comprehensive review of the existing literature pertaining to the effects of resistance training on morphological adaptations, specifically hypertrophy, as well as physiological adaptations including muscle strength and vascular function, as well as the current state of knowledge regarding blood flow restriction. The review will be presented in the following order:

1. Mechanisms of muscle hypertrophy
2. Measurement of muscle hypertrophy
3. Mechanisms of muscle strength
4. Physiology of blood flow restriction resistance training
5. Application of blood flow restriction
6. Cardiovascular risks from resistance training and blood flow restriction
7. OMIN-RES

1. Mechanisms of muscle hypertrophy

Human skeletal muscle is one of the most adaptable tissues in the body, capable of significant responses to mechanical and metabolic stimuli (Frontera & Ochala 2014). The overall size of a muscle is primarily determined by the number and size of individual muscle fibers. Muscle hypertrophy occurs through an increase in the size of these fibers, a process known as ***myofibrillar hypertrophy*** (Taber et al. 2019), rather than through an increase in the number of fibers, ***hyperplasia*** (Glass 2005). Muscle hypertrophy has been extensively studied and measured using various methods, including muscle girth (e.g. Coratella & Schena 2016), anatomical cross-sectional area (e.g. Moore et al. 2012; Farup et al. 2014), muscle thickness (e.g. Kim et al. 2015; Timmins et al. 2016), muscle volume (e.g. Blazevich et al. 2007; Franchi et al. 2014), fiber type area (e.g. Hortobagyi et al. 2000; Vikne et al. 2006), and fat-free mass/lean mass analysis (e.g. English et al. 2014; Franchi et al. 2015).

Furthermore, the complexity of measuring hypertrophy increases when considering the different types of muscle growth, particularly after certain resistance training protocols. While hypertrophy is often associated with an increase in individual muscle fiber size, there is another type known as ***sarcoplasmic hypertrophy***. This form of hypertrophy involves a greater expansion of the sarcoplasm, the fluid, and non-contractile components within muscle fibers, rather than an increase in the contractile proteins themselves (Roberts et al. 2020). For example, Haun et al. (2019) demonstrated that the resistance training program that was very high in volume set (32set per muscle group per week) resulted in significant sarcoplasmic hypertrophy in trained young men over a 6-week period.

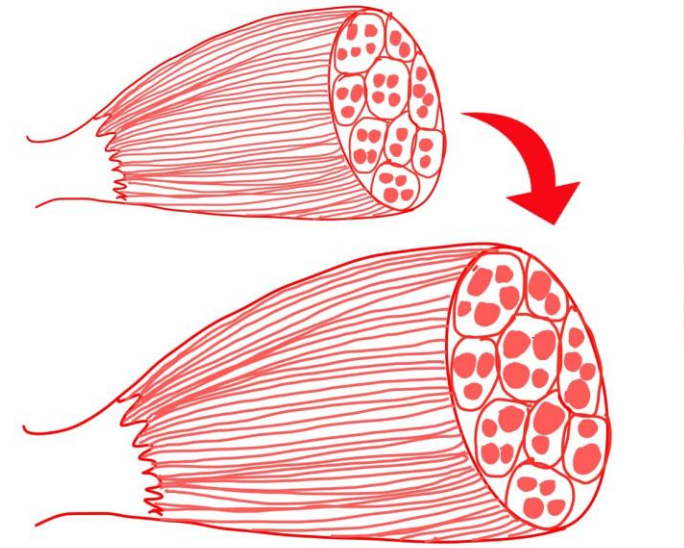


Figure 2. Myofibrillar hypertrophy

Although our understanding of muscle hypertrophy mechanisms has greatly expanded, it remains incomplete. Current consensus identifies three primary factors that likely initiate muscle hypertrophy in response to resistance training: mechanical tension, metabolic stress, and muscle damage (Schoenfeld 2010). While a comprehensive review of each factor is beyond the scope of this dissertation, the focus will be on ***mechanical tension*** and ***metabolic stress***, which are considered the most significant stimuli for hypertrophy.

1.1 Mechanical tension

Firstly, mechanical tension is considered to be the most important driving factor for inducing muscle hypertrophy (Schoenfeld 2016). To simplify this term, the mechanical tension refers to detection of tension occurring within the muscle cells as the result of the force generation of individual muscle fibers either by shortening contraction or lengthening contraction. This imposed tension causes the disturbance in the integrity of skeletal muscles and it is censored by the ***mechanoreceptor*** (Schoenfeld 2021). From literature to date, the mechanoreceptor is still unclearly defined. The potential mediators included integins, titins, and myonuclei that can detect the produced force, rendering skeletal muscle to hypertrophy (Schoenfeld 2021). Subsequently, these mechanoreceptors convert the mechanical stimuli into a cascade of electrochemical signaling, called ***mechanotransduction***, to promote increased muscle protein synthesis and decreased muscle protein breakdown (Grigg 1986; Zou 2011). The maintenance of skeletal muscle mass is depending on the regulation of the balance between anabolic and catabolic processes. ***If the rate of muscle protein breakdown, catabolism, exceeds the rate of muscle protein synthesis, anabolism, we tend to lose some muscle mass and vice versa.***

One of the key regulators of muscle protein synthesis in human body is special complex protein kinase known as ***the mammalian target of rapamycin (mTOR)*** (Yoon 2017). mTOR has been identify as a growth factor that controls the protein translational machinery and cell growth (Hornberger & Chien 2006). Activation of mTOR from tension-induced factor such as resistance training can cause the internal environmental changes in the intracellular level within the muscle cell, regulating the muscle protein synthesis, causing the anabolic process to be enhanced, and decreasing the rate of muscle protein breakdown (Laplante & Sabatini 2012). Study has shown that the mechanical tension from resistance training activity had potentially sufficed to directly stimulate the muscle protein synthesis via the activation of mTOR alone. For example, Kazior et al. (2016) compared the effect of the resistance training only by doing leg press at 70% of 1RM and the resistance training in combination of endurance cycling. The results showed that both training paradigms led to the enhancement of the content of mTOR protein. The author concluded that the addition of endurance exercise did not compromise the anabolic stimuli from resistance training but the content of mTOR could also increase by only resistance training.

The activation of mechanotransduction can induce several molecular signaling cascades that regulate either muscle protein synthesis, or muscle protein breakdown, or both (Lim et al. 2022). One of the most well-accepted molecular signaling that directly related to the mechanical tension mediating the activation of mTOR is through the Insulin-like growth factor-1/Phosphatidylinositol-3 kinase/Protein kinase B pathway (***IGF-1/PI3K/Akt pathway***) (Hornberger et al. 2004; Laplante & Sabatini 2012; Wackerhage 2014). The end result of activation of this pathway is increasing the muscle protein synthesis and degrading the muscle protein breakdown (Glass 2005; Schiaffino & Cristina 2011). Besides, the sensitivity of the mechanosensor appears to be dependent on the tension imposed on the muscle tissue. So, according to Schoenfeld (2016), the factors influencing the mechanosensor include the intensity of training and the duration of loading, by manipulating these variables indirectly mediating intracellular signaling, resulting in the hypertrophic adaptation

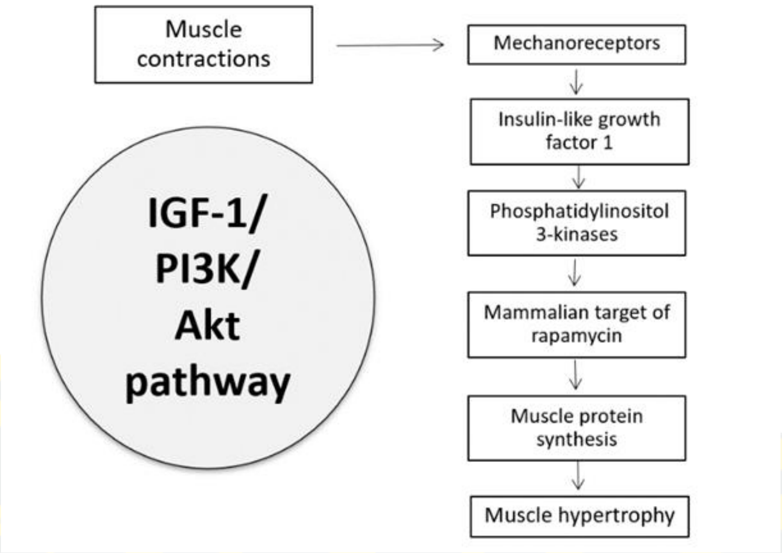


Figure 3. IGF-1/PI3K/Akt pathway

In specific, as its name suggests, this signaling pathway starts with the growth factor, ***IGF-1***, releasing from contracting muscles during exercise. The mechanical tension up-regulates in the productions of the ***IGF-1 hormone*** (Schoenfeld 2010). IGF-1 exists in three different isoforms which may play different role in muscle hypertrophy; ***IGF-1Ea***, ***IGF-1Eb***, and ***IGF-1Ec*** (Philippou et al. 2009). According to the literature, the role of IGF□1Ea can promote the satellites cell differentiation while the IGF□1Eb is responsible for activation of the satellite cell and proliferation (Ascenzi et al. 2019). The IGF-1Ec is alternatively known as ***the mechano-growth factor (MGF)*** which sensitively responds to mechanical stimulation (Schoenfeld 2010). That is to say, without the mechanical tension, this isoform will not be elevated. For example, study has examined the expression of IGF-1 isoforms in 3 different contexts. The first group that received the human growth hormone administration only showed the increases in IGF-1Ea and IGF-1Eb, but IGF-1Ec remained unchanged despite the fact that human growth hormone can indirectly induce the production of the IGF-1 in liver and other target tissues (Olarescu et al. 2019). However, the groups that performed resistance and combined with growth hormone administration demonstrated the increases of all 3 isoforms (Hameed 2004). Stimulating this MGF results in inducing muscle anabolic environment through activating this signaling cascades, IGF-1/PI3K/Akt.

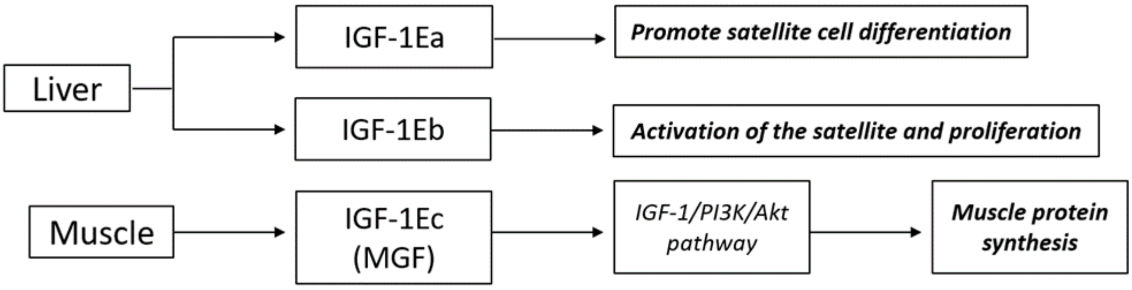


Figure 4. IGF-1 isoforms. IGF-1Ec or Mechano-growth Factor is local IGF-1 which stimulate muscle protein synthesis and hypertrophy.

Moreover, when IGF-1/PI3K/Akt is activated, there are two distinct protein complexes of mTOR activations. The first protein complex is known as ***the mammalian target of rapamycin complex 1 (mTORC1)*** (Wackerhage 2014). The function of mTORC1 once activated centers around the synthesizing of muscle protein, or more scientifically termed translation initiation and elongation of muscle protein. Technically, protein is synthesized by ribosomes and mTORC1 does modulate these ribosome functions and ribosome biogenesis (Wackerhage 2014). Besides, the mTORC1 can be blocked by pharmacological agent known as Rapamycin. Rapamycin is a drug that antagonizing mTORC1 and reduces its hypertrophy-promoting effect, even after RT (Schoendfeld 2021). A study had showed that muscle protein synthesis after RT was significantly blunted after Rapamycin administration in humans. In a study, one of two groups of healthy male participants received 12 mg (around 0.15mg/kg bodyweight) of Rapamycin for 2 hours prior to exercising and then performed leg extension exercise for total 110 repetitions at 70% of their 1RM. The muscle biopsy results showed that muscle protein synthesis post-exercise in the group receiving Rapamycin was not increased, while significantly increased in control group by 40% higher from pre-exercise (Drummond et al. 2009). Therefore, it is generally accepted that activation of mTORC1 is indispensable for increasing muscle protein synthesis. Sometimes mTORC1 is referred in literature as the regulatory associated protein of mTOR or ***Raptor*** which is one of the many protein species composing of mTORC1 that is sensitive to Rapamycin (Goodman 2019).

Another important and distinct complex protein of mTOR, but less documented, is called ***the mammalian target of rapamycin complex 2 (mTORC2)*** (Wackerhage 2014). mTORC2 is sometimes referred as rapamycin-insensitive companion of mTOR or ***Rictor*** (Goodman 2019). As its name suggested, Rictor is insensitive to pharmacological Rapamycin and is not directly relevant to muscle protein synthesis as mTORC1 does. Briefly, mTORC2 is however regulating about the energy metabolism, insulin signaling process, and cell survival (Wackerhage 2014; Lim et al. 2022). It also can be hypothesized that the way resistance training improves insulin sensitivity and muscle glucose uptake may be partly through the activation of this mTORC2 during the exercising (Ogasawara et al. 2019). It is important to clarify that these molecular events of mTOR is about muscle producing force and equipment-independent. The numbers of studies have showed that various forms of resistance training can stimulate muscle protein synthesis and muscle hypertrophy independent of resistance forms such as free weight (Kikuchi & Nakazato 2017), elastic band (Yasuda et al. 2015), machine (Walker et al. 2013), kettlebell (Chen et al. 2018), or even suspention training (Soligon et al. 2020).

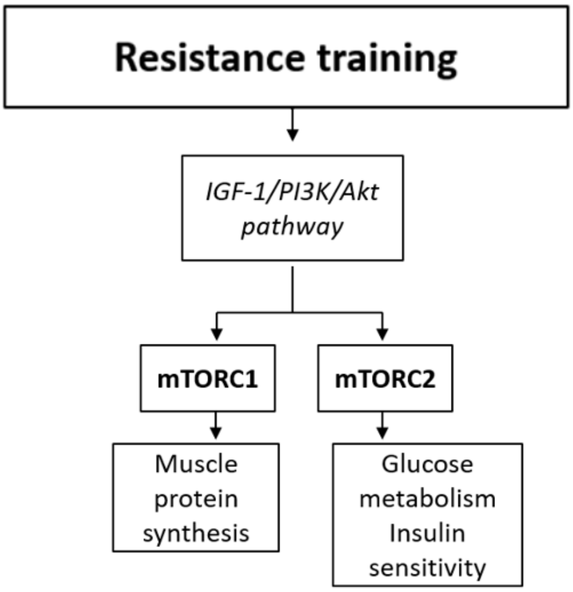


Figure 5. IGF-1/PI3K/Akt pathway stimulate mTORC1 and mTORC2.

training has also been shown to stimulate ERK1/2 effectively. Taylor et al. (2012) compared resistance training at 85% 1RM and 60% 1RM in a randomized crossover design, finding similar ERK1/2 activation for both intensities. This similarity may be attributed to the similar set duration (15-20 seconds) and corresponding mechanical and metabolic stresses experienced during the exercises. Additionally, Popov et al. (2015) demonstrated that ERK1/2 activation was 1.6-fold higher when resistance training was performed without rest between repetitions compared to with rest. Continuous muscle contractions increase metabolic stress and reactive oxygen species, while muscle oxygenation decreases, leading to greater ERK1/2 activation. However, evidence regarding resistance training and ERK1/2 activation is inconsistent. Gonzalez et al. (2016) found no significant increase in ERK1/2 with moderate intensity (70% 1RM) or high intensity (90%1RM) resistance training. In contrast, Taylor et al. (2012) observed significant ERK1/2 activation up to 6 hours post-exercise with training at 60-65% 1RM. The discrepancy between studies may stem from the number of repetitions; Gonzalez's lower repetition protocol may not induce sufficient cellular stress due to shorter time under tension. ***Training with 18-20 repetitions likely provides adequate time under tension to accumulate intracellular stress and activate ERK1/2 effectively***. Thus, TUT should be considered in program design.

In terms of muscle hypertrophy, ERK1/2 activation can increase muscle protein synthesis similar to that induced by the PI3K/Akt/mTOR signaling pathway. Winter et al. (2011) found that ***ERK and Akt work synergistically to promote mTORC1 signaling***, with combined activation enhancing mTORC1 stimulation more than either pathway alone. Additionally, ERK1/2 plays a significant role in satellite cell proliferation (Jones et al., 2001; Chen et al., 2017). Since skeletal muscle fibers are post-mitotic and rely on satellite cells for repair and regeneration, signaling pathways affecting satellite cell function are crucial for maintaining muscle health (Partridge, 2002).

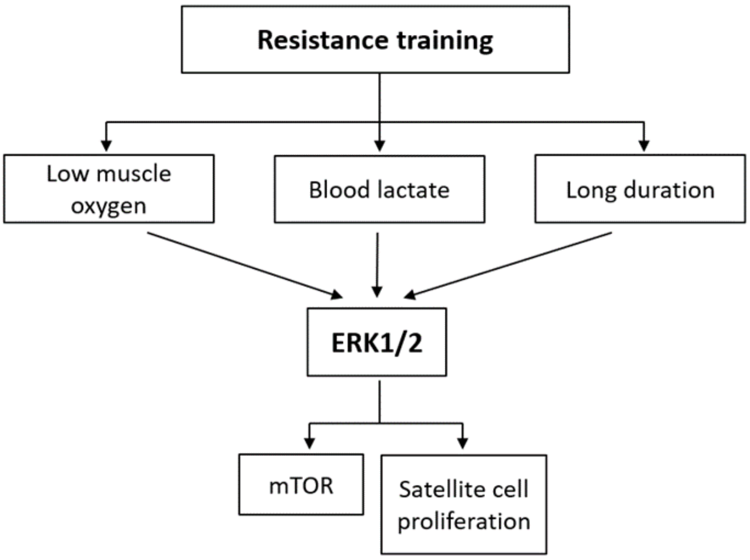


Figure 6.Resistance training stimulates ERK1/2 through several stimuli.

Next, the ***p38MAPK*** pathway, often referred to as an "***endurance factor***," is activated in response to cellular stress and plays a significant role in promoting adaptations that enhance endurance performance. This includes ***increasing glucose***

uptake in exercising muscles (Bengal et al., 2020) and ***upregulating peroxisome proliferator-activated receptor γ co-activator 1α (PGC-1α)***, a key regulator of mitochondrial biogenesis and energy metabolism (Akimoto et al., 2005).

Studies have demonstrated that brief, intense exercise with short rest intervals can robustly stimulate p38MAPK in human skeletal muscle. For example, Gibala et al. (2008) reported that in healthy, active young men, four 30-second "all-out" sprints with 4-minute rest intervals significantly activated p38MAPK. While most research on p38MAPK has focused on its role in endurance exercise, a few studies have also shown that resistance training can effectively activate this pathway. For example, Holm et al. (2010) investigated the effects of resistance training at different intensities (16%1RM vs. 70%1RM) in a knee extension exercise, using a within-subject design. They found that exercise at 70%1RM significantly increased the activation of both ERK1/2 and p38MAPK compared to 16%1RM.

Moreover, high-power resistance training has been shown to elevate p38MAPK activation. For instance, one study involving nine healthy men who performed 15 sets of 3 repetitions of a dynamic clean pull exercise at 85%1RM found a significant 3-fold increase in p38MAPK activation (Kramer et al., 2007). ***This suggests that the intensity and volume of resistance exercise are critical factors in p38MAPK activation***. Hulmi et al. (2012) further compared a strength program (15 sets of 1 repetition at 90%1RM) to a hypertrophy program (5 sets of 10 repetitions at 60-80%1RM). The study found that the hypertrophy program, which had a greater total training volume (~7680 kg vs. ~2670 kg), resulted in a higher activation of p38MAPK. This difference may be attributed to the longer time under tension and the greater metabolic stress induced by the hypertrophy protocol, leading to increased metabolite accumulation (MacDougall & Sale, 2014).

The relationship between p38MAPK signaling and muscle hypertrophy remains less well-defined compared to other pathways like PI3K/Akt/mTOR. However, emerging evidence suggests that ***p38MAPK may indirectly contribute to hypertrophy by regulating satellite cell function and facilitating muscle regeneration and repair processes*** (Segales et al., 2016; Schoenfeld, 2021). Given that, satellite cells are crucial for muscle growth and repair, particularly as skeletal muscle fibers are post-mitotic and depend on satellite cell activation for regeneration (Partridge, 2002). Additionally, p38MAPK stimulates the expression of PGC-1α, a key regulator of mitochondrial biogenesis and angiogenesis (Akimoto et al., 2005). The increase in new mitochondria and blood vessels may enhance the muscle's ability to repair and regenerate by improving energy supply and nutrient delivery to damaged tissues. Although the exact mechanisms remain under investigation, p38MAPK's role in these processes indicates its potential importance in maintaining muscle mass and function.

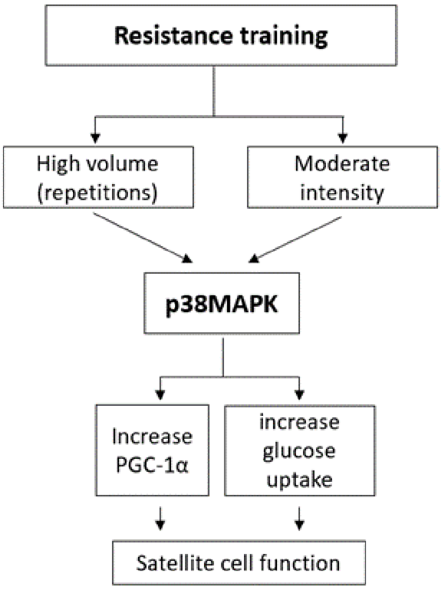


Figure 7. Resistance training stimulates p38MAPK, enhancing muscle regeneration and repair process.

Last but not least, ***JNK*** is a stress-activated signaling pathway in human skeletal muscle that responds to mechanical stress (Boppart et al., 1999). Research indicates that

JNK is particularly sensitive to the magnitude of loading. For instance, a study demonstrated that a resistance training program targeting the lower extremities, which included barbell back squats, bilateral leg presses, hamstring curls, leg extensions, and seated calf raises, significantly increased JNK activation post-exercise in resistance-trained men. This program involved 4-6 sets of 10-12 repetitions at 70% 1RM and 4-6 sets of 3-5 repetitions at 90% 1RM (Gonzalez et al., 2016). Additionally, a recent study by Eftestol et al. (2021) using a rat in-vivo strength exercise model found that muscle hypertrophy in the dorsiflexor muscles occurred in a load-dependent manner. The study revealed that acute JNK activation was highly load-specific, with elevated phosphorylation of JNK being more pronounced in the high-load group compared to the low-load group, where peak tension reached only 50–60% of that in the high-load group (Eftestol et al., 2021).

It is well-established that different contraction modes induce varying degrees of maximal force production, with eccentric contractions producing the highest force, followed by isometric and concentric contractions (Adams et al., 2004). This suggests that ***eccentric-biased training might preferentially activate JNK***, potentially contributing to greater muscle hypertrophy, as supported by meta-analytic evidence (Roig et al., 2009). At the mechanistic level, the relationship between JNK activation and muscle hypertrophy is not fully understood. However, ***there is a hypothesis that JNK might influence hypertrophy by inhibiting the Myostatin-SMAD pathway*** (Lessard et al., 2018).

Myostatin is a myokine predominantly expressed in skeletal muscle, with smaller amounts in adipose and cardiac tissue, and it is a natural negative regulator of muscle mass (Consitt & Clark, 2018). ***The muscle protein synthesis pathway (mTOR) and the muscle protein breakdown pathway (Myostatin-SMAD) function antagonistically, with one inhibiting the other*** (Wackerhage, 2014). In animal studies, mice genetically engineered to lack Myostatin exhibited approximately twice the muscle mass of normal mice (Lee, 2007). Lessard et al. (2018) hypothesized that Myostatin binds to its receptor, activating the SMAD2 signaling pathway, then translocating to the nucleus to induce muscle protein breakdown, finally decreasing myofiber size. However, heavy resistance training can activate JNK, which in turn inhibits SMAD transcriptional activity, thereby reducing Myostatin's influence and promoting myofiber growth (Lessard et al., 2018). Recent research also suggests that Myostatin inhibition, combined with resistance training, produces additive effects. A study found that Myostatin inhibition significantly increased total muscle mass in mice even without additional activity. Moreover, when combined with resistance training, a ladder climbing protocol with 50-100% maximal carrying load, and essential amino acids, this intervention further amplified Myostatin inhibition-induced muscle hypertrophy after four weeks (Jang et al., 2021).

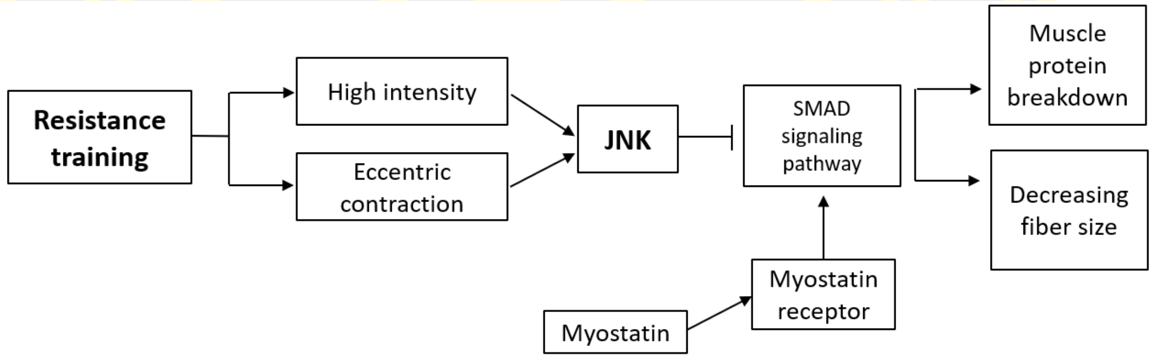


Figure 8. Resistance training activate JNK, reducing Myostatin's influence on muscle protein breakdown

Since the activation of MAPK pathways is mostly influenced by the level of cellular and metabolic stress, certain training techniques might be more effective than traditional resistance training in stimulating these pathways. Techniques like ***drop sets***, ***sarcoplasmic hypertrophy training***, ***supersets***, ***pre-exhaustion methods***, and ***blood flow restriction*** may extend the duration of sets, increasing repetition numbers and greater muscle fatigue, depleting ATP reserves and causing more cellular stress, thereby potentially enhancing MAPK activation and contributing to hypertrophy (Krzysztofik et al., 2019).

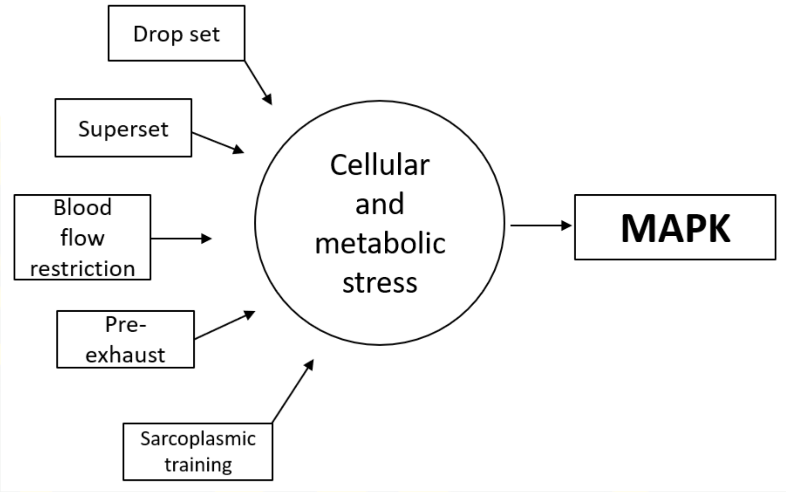


Figure 9. Resistance training techniques that enhance MAPK.

1.2 Metabolic stress

From existing evidence, the numbers of studies demonstrated that ***resistance training with high numbers of repetitions, albeit low intensity, significantly promote muscle hypertrophy comparable to high intensity resistance training with high tension*** (e.g. Tanimoto et al. 2006; Mitchell et al. 2012; Schoenfeld et al. 2015).

For example, the very early study about training intensity was conducted by Tanimoto et al. (2006), comparing 3 resistance training programs: the slow speed (3 seconds of each eccentric and concentric phase) low intensity 50%1RM, the normal speed (1 second each phase) high intensity 80%1RM, and the normal speed (1 second each phase) low intensity 50%1RM. They found that the peripheral oxygenation in muscle significantly decreased in all group as the exercise repetition starts; however, the mean value of minimum oxygenation level was significantly lower during slow speed low intensity program. The researcher suggested that this large decline in muscle oxygenation in slow speed low intensity came from the slowly continuous contractions that there was no rest interval between repetitions. Physiologically, the results of continuous contracting caused the intramuscular pressure to increase, leading to venous occlusion together with partially reducing arterial inflow, finally reducing level of oxygen delivered to muscle and increasing the accumulation of metabolites in the exercising muscle (Hwang & Willoughby 2019).

Moreover, when the level of muscle oxygenation is low, the condition known as ***muscular hypoxia*** occurs. As a result of lack of oxygen, the bioenergetic system of the body would rather shift towards the anaerobic pathway, ***glycolytic system***, which possibly results in more accumulation of metabolic byproducts such as lactate and hydrogen ion in contracting muscles (MacDougall & Sale 2014). Nevertheless, Tanimoto's study (2006) reported significant hypertrophy of muscle cross-sectional area of quadriceps after 12 weeks of training. Both slow speed low intensity and normal speed high intensity groups significantly increased their knee extensor muscle volume by 3.7-5.4% and 2.1-4.3%, respectively.

In agreement with Tanimoto's study, Mitchell et al. (2012) investigated three resistance training programs with different load and volume in legs muscle of 18 healthy men. The training legs were randomly assigned to one of three training conditions: 3sets 30%1RM, 1sets 80%1RM, and 3sets 80%1RM, with 3 training sessions per week. Afterwards, the quadriceps muscle volume was investigated. The results demonstrated that after 10 weeks of training, the quadriceps muscle volume significantly increased in all groups by 6%, 3% and 6.8%, respectively. There was no significant difference between 30%1RM and 80%1RM when the numbers of volume sets were equated (3sets). However, 1set group demonstrated the lowest hypertrophy, indicating corresponding to the dose-response relationship hypothesis between training volume and the magnitude of hypertrophic adaptation (Schoenfeld et al. 2017). In the mechanistic level, the results showed that the activation of mTOR pathway to increase muscle protein synthesis was significantly increased in all training groups at 1 hour post exercise (Mitchell et al. 2012).

Another recent study also found that both high repetition program and low repetition program elicited the same extent of muscle hypertrophy after 8 weeks of training (Schoenfeld et al. 2015). The group of researchers compared the training paradigms at different repetition ranges, 25-35 repetitions vs. 8-12 repetition per set, with 3 sets of 7 different exercises, 3 times per week. Every set of exercise was ensured that subjects achieved failure in the target repetition range. After the experiment, the muscle thickness of the bicep brachii (+5.3 vs. +8.6%, respectively), triceps brachii muscle (+6.0 vs. +5.2%, respectively), and rectus femoris muscle (+9.3 vs. +9.5%, respectively) increased significantly with no significant differences noted between groups. From the results of this study, it should be noted that the training load was not necessarily reaching to minimum 65%1RM as proposed in the training guideline for muscle growth (Ratamess et al. 2009). However, the benefit of local muscular endurance and strength were offset by each other. When measured via 50% bench press to repetition maximum, the result showed the significant increase only in the high repetition group up to 16.6% while there was no increase in low repetition group (Schoenfeld et al. 2015). Besides, when measuring muscular strength via 1RM squat and bench press, the low repetition group increased 1RM strength up to 18% and 6.9%, respectively while the high repetition group increased 1RM strength only trivially, 8.1% and 1.9%, respectively (Schoenfeld et al. 2015). So, coach and athlete who are interested in the aspect of muscle performance may bias towards these repetition zone when considering training program.

Schoenfeld et al. (2020) tested the fiber type training hypothesis, which posits that low-repetition, high-intensity training may preferentially induce hypertrophy in fast-twitch fibers, while high-repetition, low-intensity training may favor slow-twitch fibers. Their study compared low-intensity (20–30 repetitions) and high-intensity (6–10 repetitions) calf muscle training, hypothesizing that the soleus, composed of approximately 80% slow-twitch fibers, would hypertrophy more with low intensity, while the gastrocnemius, which has a balanced mix of fiber types (Johnson et al., 1973), would respond better to high intensity. However, after an 8-week program that included straight-leg and bent-leg calf raises, they found no significant difference in hypertrophy between the groups, with both the soleus and gastrocnemius muscles increasing in thickness similarly (Schoenfeld et al., 2020). These findings align with Campos et al. (2002), who also found that low (3-5 repetitions) and moderate (9-11 repetitions) intensity training led to significant hypertrophy in both type I and type II fibers, whereas high-repetition training (20-28 repetitions) did not significantly increase hypertrophy. This suggests that the fiber type-specific training hypothesis may not hold true, as both low and moderate intensities can elicit similar hypertrophic responses across fiber types (Fisher et al., 2020).

Recently, the new meta-analysis of resistance training intensity on muscle hypertrophic adaptation included 28 well-controlled studies of different intensity but performing to failure (Lopez et al. 2021). These studies were striated into group of low (<60%1RM or >15RM), moderate (60%-79%1RM or 9–15RM) and high (□80%1RM or □8 RM) intensity. The meta-analysis demonstrated that over relatively short periods of intervention, when it came to untrained and recreational individual, the extent of muscle growth were likely to be similar regardless of intensity when sets were performed to muscular failure (Lopez et al. 2021). ***Therefore, the set to failure seems to be a suitable strategy for muscle hypertrophy training for both novice men and women and both upper and lower body musculature***.

According to many examples aforementioned studies, it is noticing that ***training intensity is not the only factor contributing to muscle growth***. In the last decade, it is suggested that the associated training-induced factors that can contribute to muscle hypertrophy even when the intensity of training program is moderate or even low are referred as "***metabolic stress***" (Schoenfeld 2013; Ozaki et al. 2015; Wackerhage et al. 2018). According to Schoenfeld (2021) in the book of Science and Development of Muscle Hypertrophy, the concise definition of metabolic stress is "an exercise-induced accumulation of metabolites, particularly lactate, inorganic phosphate, and hydrogen ion". Schoenfeld (2013) purposed that there were many possible physiological responses happening as a result of metabolic stress when repeatedly contracting at moderate to high repetition numbers even when the training intensity was low to moderate that could contribute to muscle hypertrophy. Of those many, the important ones included 1) ***increased fiber recruitment***, 2) ***increased anabolic hormonal response***, and 3) ***increased cellular swelling***.

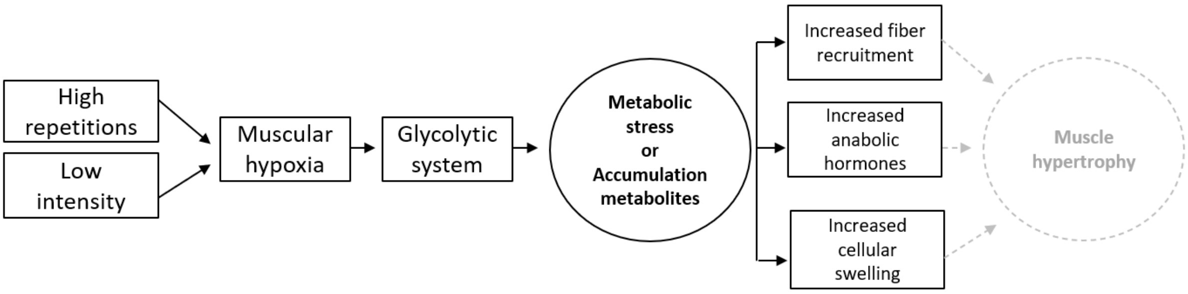


Figure 10. High repetitions and low intensity stimulate metabolic stress.

1.2.1 Increased fiber recruitment

The research suggests that resistance training induces greater muscle growth in type II fibers compared to type I fibers, emphasizing the need to engage fast-twitch fibers under tension to stimulate hypertrophy (Fry, 2004). According to Henneman's size principle, during voluntary muscle contraction, muscle fibers are recruited in order from smaller, low-threshold motor units to larger, high-threshold motor units (Henneman et al., 1965). Low-threshold motor units, which contain fewer muscle fibers and produce less force, are activated first and are sufficient for most daily activities and low-intensity exercises. In contrast, high-threshold motor units, which contain more fibers and generate greater force, are usually recruited during resistance training with heavy loads (Carpinelli, 2008). However, ***when lifting lighter loads, only low-threshold units may be engaged initially, with high-threshold units recruited later as fatigue sets in*** (Schoenfeld, 2020). During repeated contractions, even at low intensity, metabolic byproducts such as ***lactate and hydrogen ions accumulate***, ***impairing muscle contractility by reducing pH***, ***disrupting calcium release***. These cascades can result in ***hindering cross-bridge cycling fibers in working motor units***, ***leading to decreased force production*** (MacDougall & Sale, 2014; Wan et al., 2017). As low-threshold fibers fatigue, ***higher-threshold motor units are recruited to maintain the required force output*** (Burd et al., 2012).

As a reminder, skeletal muscle hypertrophy is a phenomenon when the cumulative period of muscle protein synthesis is higher than muscle protein breakdown and resistance training is an effective stimulus for the increase in this muscle protein synthesis (Damas et al. 2018). Burd et al. (2012) claimed that there were amount of evidence which suggested that lifting heavy load was not the only driver of exercise-induced rates of muscle protein synthesis. It is demonstrated that when resistance training with light load is performed to failure or/until reaching very close to failure, it will necessitate maximal fiber recruitment, as same as lifting heavy load, according to Henneman's size principle, to sustain reduced force of actively fatiguing muscle. Subsequently, ***both training with heavy load or light low until fatigue or failure will result in similar recruitment of fast twitch fibers*** and ***these additional activations will stimulate the ceiling threshold of muscle protein synthesis***. Finally, the end result is the maximal muscle protein synthesis rate occurs regardless of the intensity (Burd et al. 2012).

Moreover, Burd's explanation (2012) of fatigue and additional recruitment of high threshold motor unit was supported by many studies which found that ***when low intensity resistance training was perform until fatigue, the extent of muscle activation, as showed by electromyography (EMG), significantly increased as same as high intensity resistance training***. For example, Keogh et al. (1999) investigated the bench press training between moderate intensity (55%1RM) with fatiguing protocol – 5 second of each concentric and eccentric phase and normal speed traditional high intensity training (about 80%RM). The EMG demonstrated that for the first repetition, the mean percentage of concentric activation of pectoralis major was 76.21% in heavy bench press while only 62.98% in first repetition of moderate intensity training. However, as the repetition continued, the last repetition's mean EMG of heavy bench press was 92.94% while that of the moderate intensity fatiguing bench press also significantly increased up to 82.36% (Keogh et al. 1999). The increases in EMG signal in both training protocols indicated the similar progressive recruitment of additional muscle fibers to compensate the reduced force of actively fatiguing fibers from the first repetition to the last one (Henneman et al. 1965).

Another study to supported Burd's explanation on effect of fatigue on muscle fiber recruitments was done by Morton et al. (2019). The group of researchers investigated the EMG and glycogen content in muscle fiber of both type I and type II between training at 80%1RM and 30%1RM. They found that the initial peak EMG of high load group was 66% while that of low load group was 46%. However, as the repetition continued to failure, the final peak EMG of the high load group increased up to 90% while that of low load group increased up to 79% (Morton et al. 2019). Although the level of EMG was still higher in high load group, the magnitude of increased activations in both groups suggested the progressive recruitment of additional fibers to compensate required force until the last repetition was accomplished (Burd et al. 2012). Besides, when investigating the glycogen content, the glycogen depletion was observed in both type I and type II fiber in all training protocols, indicating that regardless of the load lifted (30 vs 80%1RM), when muscle was forced to repeatedly contract to failure, the activation of type II fibers was necessitated (Morton et al. 2019).

Evidence indicates that low and high intensity resistance training can similarly increase muscle protein synthesis when volume is equated. Burd et al. (2010) compared unilateral leg exercises at different loads: 90%1RM to failure, 30%1RM to failure, and 30%1RM work-matched to 90% 1RM. All groups exhibited significant increases in muscle protein synthesis 4 hours post-exercise, with mixed fractional synthesis rates rising by 3.5-fold, 3.2-fold, and 2.1-fold, respectively. Myofibrillar synthesis rates were substantially higher in the 90%1RM and 30%1RM to failure groups (301% and 279% above rest) compared to the 30% work-matched group (87%increase). The shorter time under tension and lower number of repetitions in the 30% work-matched group (14 reps with 27.1 seconds TUT) likely resulted in insufficient fiber recruitment, as this ***short time under tension and low number of repetitions might not be enough to fully engage fibers***. In contrast, high-intensity training (90% 1RM) required a high force that compelled all high-threshold fibers to engage from the start (Burd et al., 2010). Therefore, ***the necessity of fatigue and prolonged time under tension may not be requisite for effective fiber recruitment in high-intensity training***.

The importance of training to failure and maximizing fiber recruitment with low external loads was highlighted in studies by Burd et al. (2012) and Holm et al. (2008). Burd et al. (2012) compared low intensity resistance training at 30%1RM with varying levels of fatigue by altering lifting speeds. Participants' legs were assigned to either a slow lifting protocol (6 seconds per phase) or a volume-matched normal-speed protocol (1 second per phase). Both protocols involved 3 sets of leg extensions with 2 minutes of rest between sets. Despite similar external loads (31 kg vs. 30 kg), the time under tension was significantly greater in the slow protocol (total 407 seconds) compared to the normal-speed protocol (total 50 seconds). Myofibrillar fractional synthesis rate was significantly elevated by 2.3-fold above baseline at 24-30 hours post-exercise only in the slow protocol group, suggesting that ***greater local muscular fatigue leads to more complete fiber recruitment and increased muscle protein synthesis***. Similarly, Holm et al. (2008) demonstrated that training to failure or with high fatigue levels is crucial for maximizing muscle growth. Using a within-subject design, they compared the effects of low intensity training at 15.5%1RM with 36 repetitions per set (separated by 5 seconds each) and high-intensity training at 70%1RM with 8 repetitions per set. After 12 weeks of training, quadriceps muscle cross-sectional area was measured. The low intensity group showed significantly smaller hypertrophy, only about 2% increase, compared to the high-intensity group (about 8% increase). ***This indicates that even though low intensity training included more repetitions, the extended inter-repetition rest periods reduced fatigue accumulation, limiting motor unit recruitments, and consequently reducing muscle hypertrophy***, whereas high-intensity training with continuous exertion was more effective (Holm et al., 2008).

The mechanism by which high level of local fatigue supported the increased motor unit recruitment through low intensity resistance fatiguing protocol enhancing muscle hypertrophy was further strengthened by many studies with the application of blood flow restriction technique (e.g. Abe et al. 2005; Kubo et al. 2006; Fujita et al. 2008; Kacin & Strazar 2011; Libardi et al. 2015; Ellefsen et al. 2015).

In ***blood flow restriction resistance (BFR)*** training research, typical intensities range from 15% to less than 50% 1RM (Mattocks et al., 2018). An early study by Abe et al. (2005) highlighted the effects of low intensity training with and without BFR. Sixteen healthy men performed squats and leg curls at 20%1RM twice daily for 12 days. Participants were divided into a low intensity group and a low intensity BFR group, the latter using an elastic cuff with a starting pressure of 160 mmHg, increasing by 10 mmHg daily. Both groups completed 15 repetitions per set for 3 sets of each exercise. After 12 days, the BFR group showed a significant increase in mid-thigh muscle cross-sectional area (8.5%) compared to the low-intensity group (1.8%). Specifically, the rectus femoris and biceps femoris volumes increased by 7.7% and 10.1%, respectively, in the BFR group, while the low intensity group saw minimal changes (+1.4% and +1.9%, respectively). Additionally, the BFR group experienced a 9.1% increase in gluteus maximus muscle cross-sectional area. ***The enhanced hypertrophy observed in the BFR group can be attributed to increased fatigue resulting from restricted venous outflow and metabolite accumulation***. This heightened fatigue likely led to greater recruitment of muscle fibers, particularly type II fibers, to compensate for the reduced force production and maintain tension during exercise (Pearson & Hussain, 2014). However, the short study duration limits the ability to distinguish between true hypertrophy and potential muscle edema (Koh & Pizza, 2009), suggesting that longer training periods, such as more than 6 weeks, may be necessary to accurately assess muscle growth (Damas et al., 2018).

In line with the findings of Abe et al. (2005), Kacin and Strazar (2011) examined the effects of blood flow restriction (BFR) training over a longer period, conducting 16 sessions in 4 weeks with 10 recreationally trained male college students. Their protocol involved 4 sets of unilateral knee extensions at 15%1RM. One leg was subjected to a BFR fatiguing protocol, performing to volitional failure, while the other leg followed a free blood flow protocol with the same number of repetitions as the BFR leg. The BFR cuff pressure was set at 230 mmHg. Results indicated significant increases in muscle cross-sectional area for the rectus femoris (9.3%), vastus lateralis (6.7%), and vastus medialis (4.5%) in the BFR leg, whereas no significant changes were observed in the free blood flow leg. Additionally, the maximal number of repetitions in a knee extension test increased by 63% (from 44 to 71) in the BFR leg and by 36% (from 45 to 60) in the free blood flow leg, with the BFR leg showing a significantly greater improvement. This study demonstrated that BFR training not only enhances muscle mass but also improves local muscular endurance. Notably, the BFR leg significantly exhibited a 45% higher EMG amplitude of the rectus femoris muscle during the final repetition of the maximal repetition test, suggesting greater recruitment of higher-threshold motor units (Burd et al., 2012; Morton et al., 2019). ***The lack of significant fatigue and failure in the free blood flow leg likely resulted in lower fiber recruitment and reduced hypertrophic adaptation compared to the BFR protocol***

In summary, low intensity resistance training with high repetitions can achieve muscle hypertrophy comparable to high intensity training, provided that it induces sufficient metabolic stress and local muscular fatigue. Studies indicate that when low intensity resistance training is performed to failure or very close to failure, it recruits high-threshold motor units and type II fibers, leading to significant muscle protein synthesis (Schoenfeld et al., 2021). Conversely, low intensity resistance training that does not induce substantial local fatigue often fails to maximize fiber recruitment and muscle growth. ***Thus, muscle hypertrophy seems to be intensity-independent as long as the training reaches a high level of fatigue*** (Lasevicius et al., 2018; Morton et al., 2019).

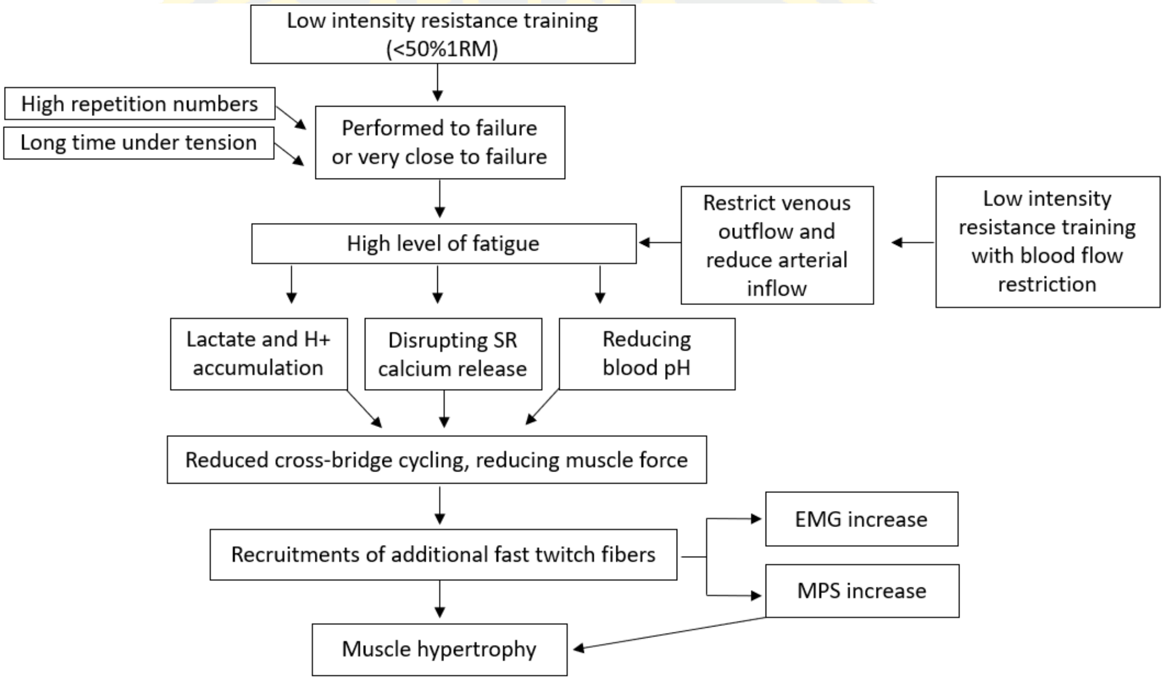


Figure 11. How low intensity resistance training increases recruitments of fast twitch fibers and hypertrophy.

1.2.2 Increased anabolic hormonal response

The role of hormone in modulating skeletal muscle hypertrophy is still contentious. When considering the roles in muscle hypertrophy, hormones are technically classified into 2 groups; ***anabolic hormones*** and ***catabolic hormones*** (Fink, Schoenfeld & Nakazato 2018). In simple words, ***anabolic hormones are related to muscle building and increased muscle protein synthesis*** such as testosterone, growth hormone, and IGF-1 while ***catabolic hormones are those related to muscle wasting and decreased muscle protein synthesis*** such as cortisol (Schoenfeld 2010). It was purposed that elevation of anabolic hormones post resistance exercise might play a role in facilitating muscle hypertrophy such as increase protein metabolism and satellite cell function (Crewther et al. 2006).

Since the early 1990s, it has been observed that hypertrophy-oriented training, as defined by the ACSM - moderate intensity (70-85%1RM), moderate repetitions (8-12 per set), and short rest intervals (60-120 seconds) - significantly upregulates acute muscle-building hormone responses (e.g., Hakkinen & Pakarinen 1993; Gotshalk et al. 1997; Kraemer et al. 1998; McCall et al. 1999). Hakkinen and Pakarinen (1993) conducted a seminal study examining serum growth hormone and testosterone levels in 10 elite male strength athletes under different training conditions. Using a crossover design, participants performed two squatting protocols: a heavy workout (20 sets of 1RM) and a moderate workout (10 sets of 10RM) with 3-minute rest intervals. The study found significant hormonal differences between the conditions. In the moderate workout, serum testosterone increased significantly (from 23.1 to 28.6 nmol/l), while no change was observed in the heavy workout. Additionally, serum free testosterone rose significantly only after the moderate workout (from 65.8 to 80.6 pmol/l). Although both conditions increased serum growth hormone, the rise was far greater in the moderate workout (from 0.16 to 27.7 ug/l) compared to the heavy workout (from 0.31 to 1.43 ug/l). Blood lactate levels, indicating metabolic stress, were also significantly higher in the moderate workout than in the heavy workout (15 mmol/l compared to 3.5 mmol/l, respectively). ***This suggests that the moderate workout 10sets of 10 reps, with higher repetitions and longer time under tension, induced greater metabolic stress***. Physiologically, one potential reason was likely due to lower oxygen tension in the muscles when volume per set was high (Schoenfeld 2013).

In alignment with Hakkinen and Pakarinen's findings, Gotshalk et al. (1997) compared acute hormonal responses to 1-set versus 3-set heavy resistance exercise protocols, focusing on serum growth hormone, testosterone, and blood lactate. The study involved eight well-trained participants with an average of 6.2 years of resistance training experience. Two heavy resistance training protocols were utilized: 1 set of each exercise at 10RM and 3 sets of each exercise at 10RM, with a 1-minute rest interval between sets. The exercises targeted all major muscle groups, including bench press, leg extension, military press, sit-ups, seated row, pulldown, arm curl, and leg press. The total work was estimated at 19,821 Joules for 1 set and 58,272 Joules for 3 sets. Blood analysis revealed that growth hormone concentration significantly increased post-exercise, with a more substantial response observed in the 3-set protocol (+700%) compared to the 1-set protocol (+400%). Similarly, serum testosterone levels showed a significantly higher increase in the 3-set protocol (+32%) than in the 1-set protocol (+14%), with statistical significance at immediately, 5-, 15-, and 30-minutes post-exercise (all significant different from baseline). The study concluded that ***the total work performed during exercise is a key factor in endocrine responses during the acute post-exercise period***, suggesting that higher set volumes may enhance hormonal response (Gotshalk et al. 1997).

Another study supporting the relationship between total work and hormonal response was conducted by Smilios et al. (2003), which examined the effect of the number of sets on serum hormones during an endurance training protocol. In this study, 11 young, healthy men with 2-8 years of resistance training experience participated. The protocol included four exercises: bench press, lat pulldowns, squat, and overhead press, performed at 30-60%1RM for 15 repetitions per set, with a 1-minute rest between sets and a 6-minute rest between exercises. On the first occasion, participants performed 2 sets of each exercise, and on the next occasion, they performed 4 sets. The estimated training time was 30-35 minutes for 2 sets and 50-65 minutes for 4 sets. Results showed that peak blood lactate immediately post-exercise was approximately 10-12 mmol/L, significantly different from the control session. The serum growth hormone levels increased more significantly in the 4-set training compared to the 2-set training at both immediate and 15 minutes post-exercise (approximately 13 µg/L and 21 µg/L, respectively). The total work performed between the 2-set and 4-set protocols was nearly doubled (38,362 vs. 69,757 Joules, respectively) (Smilios et al. 2003). ***This suggested that the number of sets might influence long-term adaptations through distinct hormonal responses, indicating that higher total work may be necessary to optimize training outcomes***.

However, focusing solely on total work or volume may not accurately reflect the differences in muscular fatigue between high-fatigue and low-fatigue protocols, even when the training volume is matched. A study by Shibata et al. (2019) examined the effects of high-fatigue and low-fatigue squat protocols on acute anabolic hormone responses in 10 physically active men. The high-fatigue protocol involved 3 sets to failure, while the low-fatigue protocol matched the total repetitions but distributed them across 6 sets without reaching failure. At 75% 1RM, the high-fatigue protocol resulted in an average of 15.0±1.1, 10.7±1.7, and 8.2±1.2 repetitions per set, respectively, while the low-fatigue protocol produced averages of 6.1±0.5 to 5.3±0.5 repetitions across sets. The session rate of perceived exertion was significantly higher in the high-fatigue protocol (8.4 vs. 4.1). Furthermore, growth hormone levels 30 minutes post-exercise were significantly higher in the high-fatigue protocol (12.3 ng/ml vs. 4.4 ng/ml), as was cortisol (19 µg/dl vs. 14 µg/dl). Therefore, ***when considering metabolic stress, training to failure in each set is likely to induce greater accumulated stress than training far from failure, regardless of the number of sets or total repetitions***. This was further supported by blood lactate analysis, which showed significantly higher levels in the high-fatigue protocol at all post-exercise time points (5-8 mmol/l vs. 2-3 mmol/l) (Shibata et al. 2019).

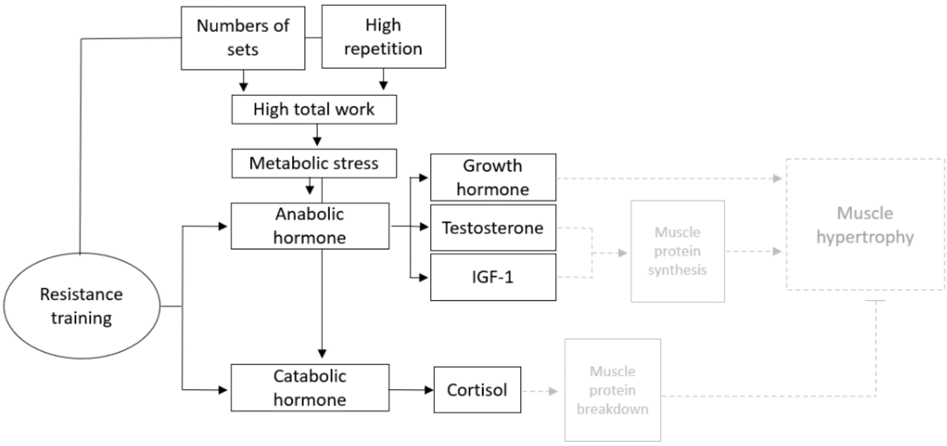


Figure 12. Resistance training influences acute release of anabolic and catabolic hormones

Interestingly, ***the blood flow restriction technique (BFR) highlights the critical role of fatigue and metabolic stress in triggering hormonal responses during low-intensity training, even when volume is matched***. Yinghao et al. (2021) investigated the effects of BFR resistance training under different pressures on endocrine responses. The study included 25 healthy male college students, with an average age of 19 years and no prior systematic training experience. Each participant underwent three resistance training protocols in a crossover design: 30%1RM without BFR (control), 30%1RM with 40% arterial occlusion pressure, and 30%1RM with 70% arterial occlusion pressure. The training program consisted of 6 sets of 15 repetitions of knee extension and knee flexion exercises, with a tempo of 3 seconds for both concentric and eccentric phases. Each protocol was separated by 72 hours to avoid fatigue effects. The results showed that the 30%1RM load was approximately 57 lbs, and the occlusion pressures were 78 mmHg for 40% and 137 mmHg for 70% occlusion. Blood lactate levels in the 70% occlusion pressure group were significantly higher than those in the 40% occlusion pressure and control groups, with the 40% group also showing significantly higher levels than the control. The effect size increase in blood lactate was 106%, 265%, and 507% in the control, low, and high occlusion pressure groups, respectively. Similarly, growth hormone levels were significantly higher in the high occlusion pressure group at all post-exercise time points compared to the low occlusion pressure group, with the low occlusion group also showing higher levels than the control. The effect size increase in growth hormone was 775%, 980%, and 1625% in the control, low, and high occlusion pressure groups, respectively. Moreover, the effect size increase in level of IGF-1 was 2%, 4%, and 11% in control, low and high occlusion pressure group, respectively. Lastly, testosterone levels also showed a significant increase, with effect sizes of 4%, 15%, and 25% in the control, low, and high occlusion pressure groups, respectively. The clear findings of Yinghao's study suggest that ***higher BFR pressures lead to greater metabolic stress within the muscle, resulting in a more pronounced anabolic hormonal response***. Even when resistance training was matched for load, repetitions, or workload, protocols that induced the highest levels of fatigue and metabolic stress produced the greatest hormonal responses (Schoenfeld et al. 2010).

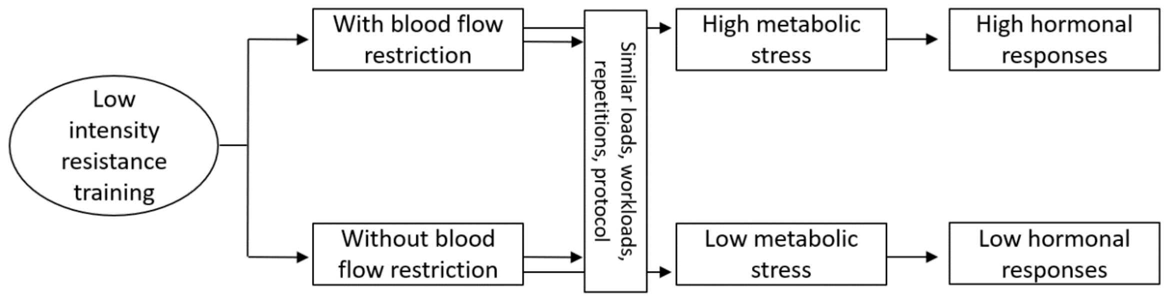


Figure 13. Resistance training with blood flow restriction stimulate more metabolic stress even similar loads, workloads, repetitions, or protocol.

Nevertheless, it is important to consider that most studies measuring hormonal responses to exercise focus on the acute period (e.g., immediately, 5- or 15-minutes post-exercise). However, ***muscle hypertrophy results from chronic training, and changes in acute hormonal responses may not accurately reflect long-term basal hormone concentrations***. For example, McCall et al. (1999) provided evidence that while muscle hypertrophy was observed after 12 weeks of training, basal hormone concentrations remained unaffected. The study examined the chronic hormonal response to a resistance training program specifically designed to induce muscle hypertrophy in 11 healthy college men. The participants trained three times per week, performing 3 sets of 10 repetitions with 1-minute rest intervals across 8 exercises per session. Serum levels of anabolic hormones were collected before and after 12 weeks of training. The results showed significant increases in muscle strength and hypertrophy after 33 training sessions, with 1RM forearm flexor strength increasing by 25% and the cross-sectional area of the biceps brachii increasing from 11.8 to 13.3 cm^2. Additionally, muscle biopsy samples revealed increases in type I fiber area from 4196 to 4614 µm^2 and type II fiber area from 6378 to 7474 µm^2. Despite these adaptations, basal hormone levels remained unchanged (growth hormone from 1.20 to 0.12, IGF-1 from 26.1 to 26.4, testosterone from 18.3 to 17.9, pre- to post-training, respectively). However, the researchers noted a correlation between the acute increase in serum growth hormone and hypertrophy of type I and type II fibers, while no such correlation was found for other hormones (McCall et al. 1999). ***Physiologically, it is understood that growth hormone can stimulate IGF-1 production, which in turn activates the mTOR signaling pathway, driving muscle protein synthesis and muscle hypertrophy*** (Schoenfeld 2020).

Another study that questioned the impact of post-exercise hormonal changes on muscle hypertrophy was conducted by West et al. (2009). In this study, the researchers manipulated the resistance training program for 12 healthy young men, assigning different training regimens to elicit varying hormonal environments. One arm of each participant was trained under a low hormonal milieu, performing only arm curls (3-4 sets of 8-12 repetitions at 95% 1RM) to voluntary failure in the final set. The contralateral arm performed the same arm curls but was followed by 5 sets of 10 repetitions of leg press and 3 sets of 12 repetitions of supersets between leg extension and leg curl at 90% 1RM, creating a high hormonal milieu. Both arms were trained on separate days, three times per week, for 15 weeks. The results showed that levels of growth hormone, testosterone, free testosterone, and IGF-1 were significantly higher at 15-minute post-exercise in the high hormonal milieu training arm, with no hormonal changes in the low hormonal milieu arm. Blood lactate levels also peaked at 10.5 mmol/L in the high hormonal milieu arm compared to 2 mmol/L in the low hormonal milieu arm. Despite the higher hormonal and metabolic stress in the high hormonal milieu, there was no significant difference in muscle hypertrophy between the two conditions after 15 weeks. The biceps brachii cross-sectional area significantly increased by 12% in the low hormonal milieu arm and by 10% in the high hormonal milieu arm. Muscle fiber analysis showed similar increases in type I and type II fiber cross-sectional areas under both training conditions (type I: 9% and 11%; type II: 21% and 24%, respectively). These findings contrast with earlier claims that post-exercise hormonal responses might enhance hypertrophic outcomes (Crewther et al. 2006). Thus, other mechanisms are needed to explain the similar hypertrophic responses observed in this study despite the differing hormonal environments.

1.2.3 Increased cell swelling

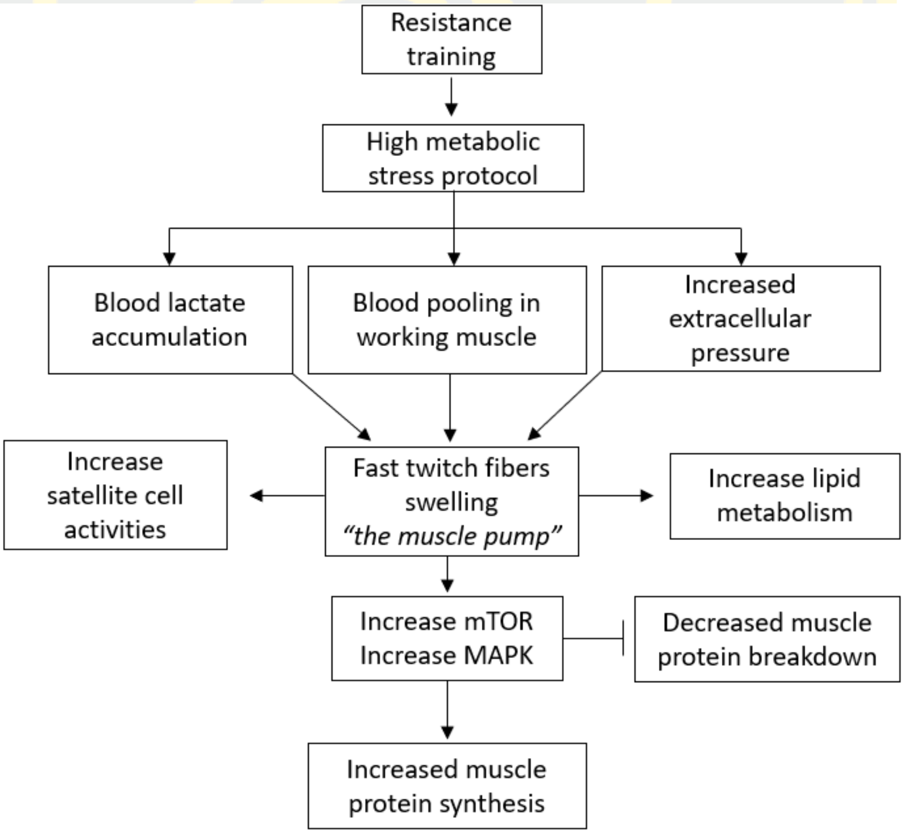


Figure 14. Effects of metabolic stress training induces cell swelling.

Cell swelling is characterized by the increase in intracellular fluid within muscle fiber (Schoenfeld 2013). This phenomenon can be detected by scientific method via the measurement of fluid-induced increased muscle thickness at immediately post-exercise by several means such as ultrasound technique or simple measuring muscle girth circumference (Wilson et al. 2013; Fortin & Billaut 2019; Thiebaud et al. 2019).

In previous studies, it was claimed that ***increased cellular hydration resulted in increase in muscle protein synthesis and decrease in muscle protein breakdown via activation of signaling pathways such as mTOR and MAPK*** (further details discussed in aforementioned section above) (Loenneke et al. 2012). Moreover, in human study, there was evidence showing that ***cell swelling also positivity affected protein metabolism by sparing of muscle protein and increasing lipolysis*** (Berneis et al. 1999; Keller et al. 2003). Moreover, Schoenfeld (2013) also proposed ***hydration-induced cell swelling was perceived as the threat to cellular integrity, triggering the signaling cascades to reinforce of cellular ultrastructure*** (e.g. increase muscle protein synthesis); moreover, ***cell swelling might further regulate satellite cell activities*** by facilitating the proliferation and fusion process which would in turn affect the long-term adaptation after training (Schoenfeld 2010). However, the mechanisms by which cell swelling increased muscle anabolism or hypertrophy needs more research to expand this understanding.

Schoenfeld and Contreras (2014) referred the exercise-induced cell swelling in their published article as "***the muscle pump***". Mechanism was claimed that resistance training of some type, especially high numbers of repetitions with low to moderate intensity, was potential to induce the alteration of intracellular-extracellular fluid balance. When muscle contractions were repeated for over a certain period of time and inducing the compression of vein that was expected to taking the deoxygenated blood out of the working muscle together with increasing arterial inflow to the working muscle to supply to needed oxygen, the intramuscular concentration of blood plasma substantially increased. At the point, the working muscle was being pooled with blood.

As a result, the concentrate plasma might leak out from the capillaries and get into the interstitial spaces. The increased plasma in the interstitial space caused the increase in extracellular pressure which in turn struggled to push the fluid back into the muscle cell. Here was where the phenomenon of muscle pump occurred because ***the working muscle was soaked with increase of intracellular fluid level*** (Schoenfeld and Contreras 2014).

Moreover, research has shown that the magnitude of the muscle pump can be amplified by resistance training protocols that promote the accumulation of blood lactate, due to its osmotic properties (Usher-Smith et al. 2006). ***Fast-twitch muscle fibers are particularly sensitive to osmotic changes and swelling because they contain a higher density of water-transporting channels known as aquaporin-4***. Aquaporin-4 is a type of aquaporin channel that facilitates the movement of water across cell membranes, playing a crucial role in regulating water homeostasis within the muscle cells. These channels are particularly abundant in the plasma membrane of fast-twitch muscle fibers, which contributes to their increased responsiveness to fluid shifts and swelling during high-intensity exercise (Frigeri et al. 1998). Given that fast-twitch fibers are more prone to hypertrophy compared to slow-twitch fibers (Campos et al. 2002), ***the enhanced cell-swelling effect induced by such resistance training protocols could be a significant mechanism regulating muscle growth*** (Rolnick & Schoenfeld 2020).

Considering resistance training program, some training variables might be adjusted for eliciting training-induced cell swelling. For example, ***the number of repetitions per set is one of the most critical variables that could enhance the muscle pump*** (Viecelli & Aguayo 2022). For hypertrophy training, the ACSM recommends performing 8-12 repetitions per set (Kraemer et al. 2002), while the NASM suggests 6-12 repetitions per set (Haff & Triplett 2016). Mechanistically, when the working muscle repeatedly contracts over time, it partly generates ATP from anaerobic energy systems (MacDougall & Sale 2014). The byproducts of this bioenergetic pathway include increased production of metabolites such as lactate, adenosine, hydrogen ions, and inorganic phosphate. If muscle contractions are sustained with increasing repetitions, these metabolites accumulate within the working muscle due to venous compression, leading to blood pooling (Schoenfeld and Contreras 2014). Given that lactate is one of the most produced metabolites, it may particularly enhance cell swelling, especially in fast-twitch fibers.

A study comparing two resistance training protocols - one with low repetitions and one with high repetitions - highlighted the significance of repetition numbers on blood lactate production (Mangine et al. 2015). Researchers randomly assigned 29 participants to either a low or high repetition group. The training intensity was notably higher in the low repetition group (90%1RM) compared to the high repetition group (70%1RM). Participants in the high repetition group performed 4 sets of 10-12 repetitions per set, while those in the low repetition group performed 4 sets of 3-5 repetitions per set. The acute metabolic response, measured via blood samples immediately post-exercise at weeks 3 and 10, revealed significantly higher blood lactate levels in the high repetition group compared to the low repetition group at both time points (12.66 vs. 6.66mmol/L, $p<0.001$ and 12.30 vs. 7.88mmol/L, respectively). ***Given that the high-repetition group trained at a significantly lower intensity—20% less than the low-repetition group—these results indicate that total repetitions may be more critical than intensity for achieving intense metabolic stress***.

Moreover, ***advanced resistance training techniques that increase the number of repetitions per set may further amplify lactate production***. For example, the ***drop set technique***, also known as the breakdown technique, involves performing dynamic repetitions until momentary muscle failure is reached, followed by an immediate reduction in load. The exercise continues with the reduced weight until failure is reached again (Schoenfeld 2020). The extent of load reduction can vary across studies, typically ranging from 20-30% of the initial load (Fisher et al. 2016; Angleri et al. 2017; Fink et al. 2017). In a study by Fink et al. (2018), the use of the drop set technique led to a significant increase in triceps brachii muscle cross-sectional area (+10%) after six weeks, compared to traditional resistance training, which resulted in a +5% increase. The study randomly assigned 16 participants to either the drop set group or a traditional training group. The drop set group performed a single set of 12 repetitions to failure, then reduced the load by 20% and continued to failure for three successive reductions. This group achieved an average total repetition volume of 38 repetitions per set. In contrast, the traditional training group performed 12 repetitions per set across 3 sets. Despite similar blood lactate levels immediately post-exercise between the two groups, the drop set technique led to a significantly greater acute increase in muscle thickness of the triceps brachii (+18.3%) immediately after exercise, while the traditional training group showed a less pronounced change (+4%). This substantial increase in muscle thickness after drop set training exemplifies the training-induced cell swelling phenomenon (Schoenfeld and Contreras 2014) and suggests that metabolites beyond lactate may also contribute to cellular swelling.

Another two training techniques that can increase the number of repetitions per working set are the ***superset technique*** (Sabido et al. 2016) and the ***tri-set technique*** (Weakley et al. 2017). Superset training involves performing a pair of different exercises in sequence without rest between them (Krzysztofik et al. 2019), while tri-set training entails completing three exercises consecutively, followed by a recovery period (Sabido et al. 2016). In a study by Sabido et al. (2016), superset resistance training - where participants performed two exercises for the same muscle group back-to-back without rest (e.g., bench press followed by incline bench press) - was compared with traditional training, which involved performing each exercise with a 90 second rest interval between sets. Both protocols had similar relative intensities at 60-70%1RM. The acute effects immediately post-exercise revealed that lactate concentration was significantly higher in the superset group compared to the traditional training group (12.1mmol/L vs 9.5mmol/L, respectively). Notably, the superset training consisted of only 3 sets of exercise, while the traditional method included a total of 6 sets. This demonstrates that superset training is not only highly demanding metabolically but also a more time-efficient method.

Although the superset technique can lead to higher blood lactate concentrations and potentially greater cell swelling, the tri-set technique can induce even higher levels of lactate. Weakley et al. (2017) compared three resistance training methods: traditional, superset, and tri-set. The exercises included squat, bench press, Romanian deadlift, shoulder press, bent-over row, and upright row. In the traditional training method, each exercise was performed for 3 sets with 2 minutes of rest between sets. In the superset method, pairs of exercises were performed consecutively: squat + bench press, Romanian deadlift + shoulder press, and bent-over row + upright row, with 2 minutes of rest between each pair. The tri-set method involved performing three exercises in series: squat + bench press + Romanian deadlift, and shoulder press + bent-over row + upright row, with 2 minutes of rest between series. Blood lactate concentrations were measured at the completion of sets 6 and 12, as well as post-exercise, based on the traditional training method. At baseline, lactate concentrations were similar across groups (1.30, 1.50, and 1.40mmol/L for traditional, superset, and tri-set, respectively). At each time point, blood lactate concentrations were significantly highest in the tri-set group, followed by the superset group, and then the traditional method. Specifically, at the completion of set 6, lactate concentrations were 7.90, 9.40, and 10.40mmol/L, respectively; at the completion of set 12, they were 8.50, 10.70, and14.10 mmol/L; and post-exercise, they were 7.40, 11.50, and 13.40mmol/L. Additionally, the completion times differed significantly between groups (42.3, 24.0, and 17.7 minutes, respectively), with the tri-set technique proving to be more time-efficient than the superset technique again.

Another training variable that can be adjusted to enhance training-induced cell swelling or lactate production is the rest interval between sets. According to the ACSM's recommendations for hypertrophy training, a rest interval of 60-90 seconds between sets is suggested (Ratamess et al. 2009). However, Fink et al. (2018) explored the effects of varying training intensities and rest intervals on acute responses and long-term muscle gains. In their study, 20 young gymnastic athletes were randomly assigned to either a short rest group or a long rest group. The short rest group had a 30-second rest interval between sets, while the long rest group rested for 3 minutes. Additionally, the training intensity was lighter for the short rest group (20RM) compared to the long rest group (8RM). The training regimen included exercises for both the triceps brachii (close grip bench press, French press, and dumbbell extension) and the biceps brachii (barbell curl, preacher curl, and hammer curl). Acute measurements of cell swelling were assessed by changes in muscle thickness immediately post-exercise. Results indicated that muscle thickness of the triceps long head significantly increased immediately post-exercise in the short rest group (+35%), while the long rest group showed a non-significant increase (+13%). Furthermore, at 8 weeks post-training, the chronic adaptation was assessed via MRI scan, revealing that the short rest group experienced a significant increase in muscle cross-sectional area of 9.93% compared to 4.73% in the long rest group. ***These findings suggest that the higher metabolic stress associated with shorter rest intervals may contribute to greater long-term hypertrophic adaptation***.

Therefore, the existing literature indicates that various training variables and techniques can be employed to enhance metabolic stress, including the number of sets, repetitions, rest intervals, and specific training techniques. The methods used to assess metabolic stress depend on the research perspective and can be evaluated through multiple approaches. Among these, measuring blood lactate concentration and acute increases in muscle thickness, such as changes in the circumference of the trained muscle immediately post-exercise, are among the most reliable indicators of metabolic stress.

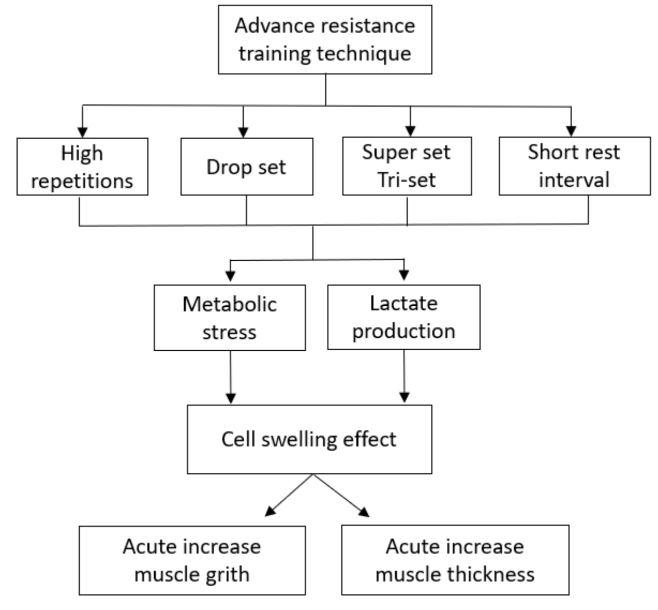


Figure 15. Advance training techniques that can enhance cell swelling.

2. Measurement of muscle hypertrophy

The word "hypertrophy" originates from the English prefix "hyper-" which means "beyond," and the Greek suffix "-trophia" signifying "growth". In the context of resistance training, skeletal muscle hypertrophy is commonly defined as an increase in muscle mass at both the cellular and whole tissue levels (Russell et al., 2000).

The concept of muscle hypertrophy has traditionally been explained as the accumulation of contractile or structural proteins, leading to an increase in the number of sarcomeres arranged in parallel within the myofibrils of existing muscle fibers (MacDougall & Sale 2014). This process leads to an expansion of the fiber area; and consequently, it would be expected that studies showing muscle growth should provide clear evidence of this phenomenon. However, while hypertrophy is a well-known adaptation to prolonged resistance training, the scientific literature reveals inconsistent findings, which often depend on the specific outcome variables being measured (Huan et al. 2019). These inconsistencies may be partly due to the variety of methods employed to assess skeletal muscle hypertrophy. Techniques like ***dual-energy x-ray absorptiometry (DXA)***, ***computed tomography scanning (CT)***, ***magnetic resonance imaging (MRI)***, and ***ultrasound imaging (US)*** are commonly used to identify regional adaptations. Also, the ***muscle biopsy technique*** has allowed researchers to compare muscle fiber size at cellular level before and after training.

Of all the measurement methods mentioned, two of the most commonly used for measuring muscle hypertrophy are ***US*** (e.g. Amirthalingam et al., 2016; Barcelos et al., 2018; Barbalho et al. 2020) and ***MRI*** (e.g. Ogasawara et al., 2013; Kubo et al., 2019). While both techniques are effective in assessing changes in muscle size, MRI is often regarded as the gold standard due to its superior accuracy and ability to provide detailed cross-sectional images of muscle tissue. This high level of precision makes MRI particularly valuable in research settings where exact measurements of hypertrophy are crucial. However, the main drawbacks of MRI are that it is time-consuming to perform on each unit and is also quite expensive, which can limit its practicality for large-scale studies (Strasser et al., 2013).

2.1 Ultrasound imaging (US)

Ultrasound imaging is a non-invasive and direct method for evaluating skeletal muscle mass. It has proven effective for assessing muscle hypertrophy (Botton et al., 2016; Brandner et al., 2019) and atrophy (Yang et al., 2019; Lee et al., 2020) in various muscles, including the biceps brachii and vastus lateralis. This imaging technique employs sound waves of varying frequencies that penetrate the body surface and traverse through tissues with differing acoustic impedances. As the sound waves encounter these tissues, they reflect back echoes that are captured by the transducer. These reflected echoes are then converted into electrical signals, which are processed to produce detailed images (O'Brien, 2007).

Numbers of variables that representing morphological changes can be obtained from US such as muscle thickness (e.g. Lanferdini et al., 2021), fascicle length (e.g. McMahon et al., 2014), fascicle angle (e.g. Ruple et al. 2022), and fascia thickness (e.g. Godwin et al., 2023).

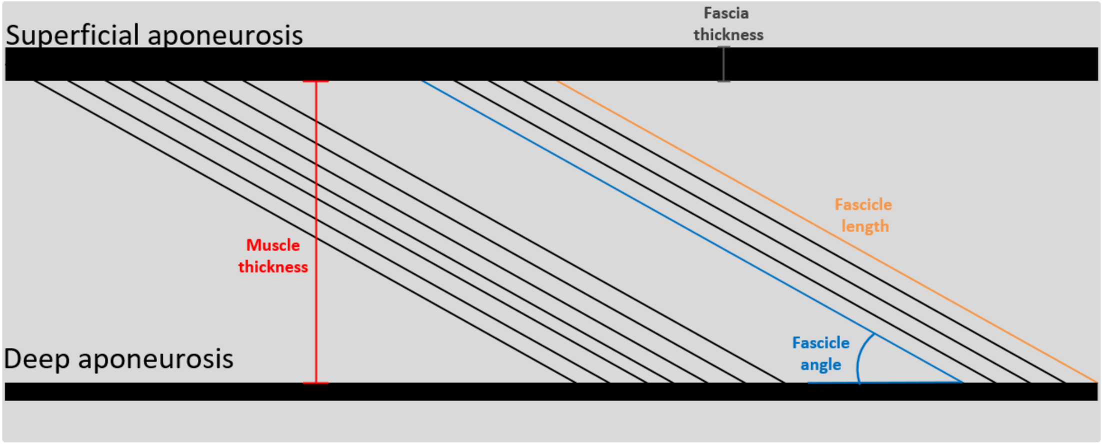


Figure 16. Graphics representing measurement of muscle thickness (Red), fascicle angle (Blue), fascicle length (Orange), fascia thickness (Gray).

Muscle thickness can be defined as the linear distance between the deep and superficial aponeurosis of the muscle of interest (Franchi et al., 2018) To measure muscle thickness, investigators often image the mid-belly of a muscle. Moreover, muscle thickness has been shown to be highly reliable in a range of muscles (intra-class correlations, or ICCs = 0.65–0.94) (Thoirs and English, 2009), it is limited in that it is only representative of one dimension of the muscle. Vigotsky et al. (2018) demonstrated that hypertrophy of different regions of the same muscle are not strongly correlated within an individual. Moreover, the angle of measurement might change the thickness of muscle. Additionally, ultrasound is highly clinician's skill-dependent, given that differences in the pressure exerted by the transducer against the skin can result in substantial variations in measurements. Thus, ultrasound-based assessments of muscle thickness though provide a fast and practical assessment of muscle size, but the quality of these assessments may vary according to rater's experience.

Numbers of previous studies have investigated ***muscle thickness of vastus lateralis*** using ultrasound imaging to investigate muscle thickness as well. For example, Alegre et al. (2006) investigated the effects of squatting exercise in 16 healthy males. Participants performed 3-4sets of 6-12 repetition at the intensity of 50-60%1RM with 180 seconds rest interval. The training frequency was 3 times per week for total 13 weeks of training. Muscle thickness was measured by US at midway between the greater trochanter and lateral condyle of the femur length. Results demonstrated that muscle thickness increased from 2.3 cm to 2.45 cm in training group, representing about 7% increase from baseline.

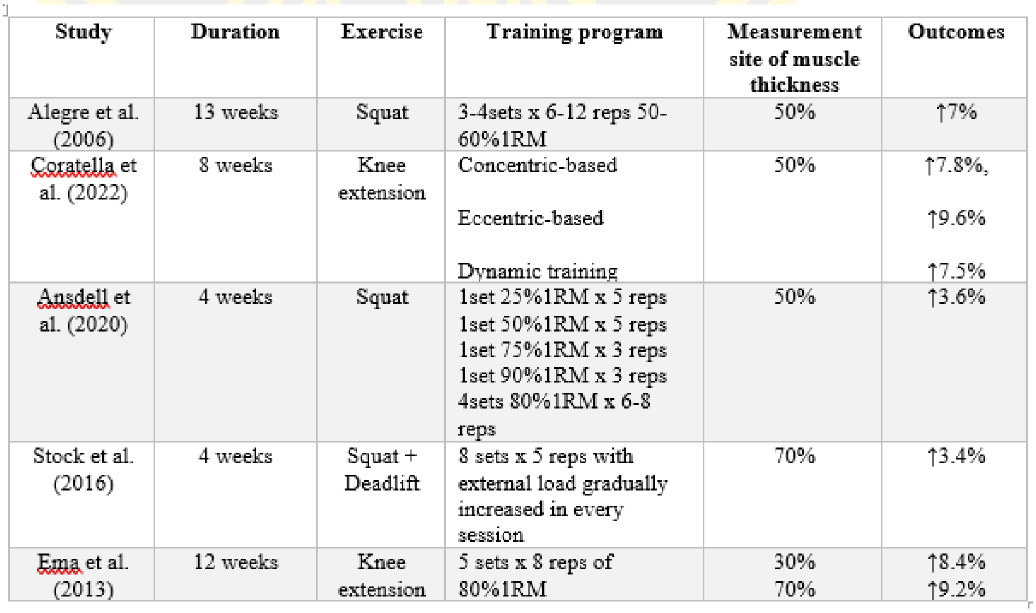
Another study that measured muscle thickness of vastus lateralis was conducted by Coratella et al. (2022). The researcher investigated effects of knee extension exercises in female participants. Participants were randomly assigned to concentric-based group, eccentric-based group, and traditional concentric-eccentric group. Training session was constructed to be 8 weeks long with 2 training session per week. Knee extension protocol consisted of 4 sets of 5 repetitions at 90%1RM with 180 seconds rest interval between sets. Muscle thickness of vastus lateralis was measured at 50% of the thigh length, determined as the midpoint between the greater trochanter and the lateral condyle of the femur. It was found that muscle thickness of vastus lateralis increased significantly to 7.8%, 9.6% and 7.5% in concentric-based group, eccentric-based group, and traditional concentric-eccentric group, respectively.

Besides, Ansdell et al. (2020) performed the interesting experiment by having participants performing 4 sets of back squatting at 25%, 50%, 75%, then 90%1RM for 5, 5, 3 and 3 repetitions, respectively. Afterwards participants performed 4 sets of 6-8repetitions at 80%1RM with 5 minutes rest between sets. Muscle thickness was then measured at 50% of vastus lateralis length. After 12 sessions in 4 weeks of training, muscle thickness increased from 22.2 mm to 23.0 mm or about 3.6%.

Similarly Stock et al. (2016) investigated back squat and deadlift training, twice a week for 4 weeks. The participants were 16 young females. Training intensity as external loads used gradually increased from session 1 to session 8 for back squat from 25.3kg, 30.5kg, 34.5kg, 37.9kg, 40.6kg, 43.5kg, 45.4kg, and 47.9kg, respectively, and for deadlift from 31kg, 37.5kg, 42kg, 44.9kg, 49kg, 51.8kg, 53.7kg, and 56.5kg, respectively. Muscle thickness of vastus lateralis was collected at about 70% of muscle length. The results demonstrated that muscle thickness increased from 2.07cm to 2.14cm or about 3.4% at post-intervention.

Moreover, as the limitation of US has been mentioned earlier that muscle thickness might varied along the length of muscle that was measured, Ema et al. (2013) investigated muscle thickness between different regions of vastus lateralis separating between proximal region and distal region. Eleven participants were instructed to performed knee extension exercise at 80%1RM for 5 sets of 8 repetitions for 12 weeks of training. Muscle thickness was measured at 35% and 70% of femur length and found that muscle thickness at 30% increased from 23.9mm to 25.9mm while muscle thickness at 70% increased from 18.5mm to 20.2mm.

Table 1. Previous studies which employed US to measure muscle thickness of vastus lateralis



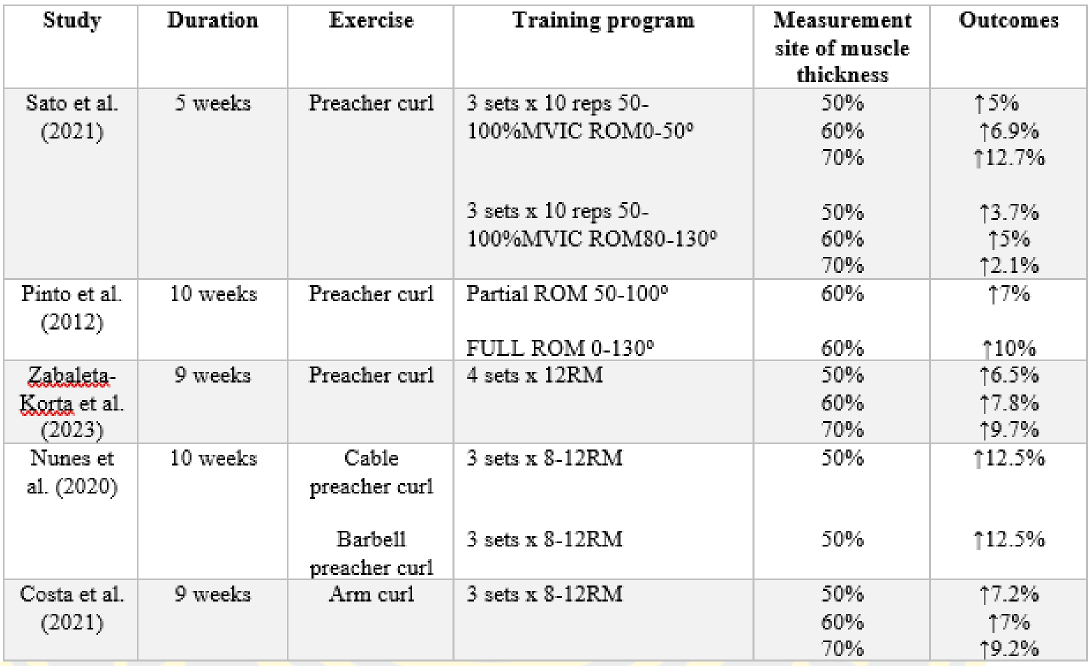
Study	**Duration**	**Exercise**	**Training program**	**Measurement site of muscle thickness**	**Outcomes**
Alegre et al. (2006)	13 weeks	Squat	3-4sets x 6-12 reps 50-60%1RM	50%	↑7%
Coratella et al. (2022)	8 weeks	Knee extension	Concentric-based Eccentric-based Dynamic training	50%	↑7.8%, ↑9.6% ↑7.5%
Ansdell et al. (2020)	4 weeks	Squat	1set 25%1RM x 5 reps 1set 50%1RM x 5 reps 1set 75%1RM x 3 reps 1set 90%1RM x 3 reps 4sets 80%1RM x 6-8 reps	50%	↑3.6%
Stock et al. (2016)	4 weeks	Squat + Deadlift	8 sets x 5 reps with external load gradually increased in every session	70%	↑3.4%
Ema et al. (2013)	12 weeks	Knee extension	5 sets x 8 reps of 80%1RM	30% 70%	↑8.4% ↑9.2%

For biceps brachii, similarly, there were previous studies as well which measuring ***muscle thickness of biceps brachii*** as a results of resistance training via US. For example, Sato et al. (2021) investigated the effect of preacher curls at different ranges of motion that one group performed at 0-50° and the other group performed at 80-130°. Muscle thickness of biceps brachii was measured at 3 region, 50%, 60% and 70% of humerus length. The results demonstrated that muscle thickness increased in every region in both training protocols.

Similarly, Pinto et al. (2012) previously investigated the effects of ranges of motion with preacher curl as well. They found that full range of motion of preacher curl from 0-130° elicited more increase in muscle thickness compared to training in range of motion from only 50-100° about +10% vs +7%, respectively. However, this study measured muscle thickness of biceps brachii at only the 60% of humerus length, which made it the weak point of this study because it lacks of the comprehensive picture of muscle growth in other area. In the same way, Zabaleta-Korta et al. (2023) compared effect of 9 weeks preacher curl exercise with dumbbell in trained females. They measured biceps brachii thickness very thoroughly at 50%, 60%, and 70% of humerus length. The results demonstrated that muscle thickness increased about 6-9% in every region, proving the effectiveness of US to measure changes in muscle hypertrophy as a result of training.

Moreover, Nunes et al (2020) compared between cable preacher curl exercise and dumbbell preacher curl exercise at similar intensity about 8-12RM. After 10 weeks of training, it was found that muscle thickness as measured from biceps brachii at 50% of humerus length increased about 12.5%, regardless of the equipment. This showed that both cable and dumbbell can be utilized to elicit hypertrophic responses from preacher curl exercise. And last but not least, Costa et al. (2021) examined effect of 9 weeks of arm curl exercise and biceps brachii hypertrophy was measured comprehensively at 50%, 60%, and 70% region. They found that muscle thickness significantly increased up to 7.2%, 7%, and 9.2% from proximal to middle and distal region, respectively. All these example studies confirmed the effectiveness of employment of US to measure change in muscle thickness of biceps brachii after a period of training

Table 2. Previous studies which employed US to measure muscle thickness of biceps brachii



Study	Duration	Exercise	Training program	Measurement site of muscle thickness	Outcomes
Sato et al. (2021)	5 weeks	Preacher curl	3 sets x 10 reps 50-100%MVIC ROM0-50º 3 sets x 10 reps 50-100%MVIC ROM80-130º	50% 60% 70% 50% 60% 70%	↑5% ↑6.9% ↑12.7% ↑3.7% ↑5% ↑2.1%
Pinto et al. (2012)	10 weeks	Preacher curl	Partial ROM 50-100º FULL ROM 0-130º	60% 60%	↑7% ↑10%
Zabaleta-Korta et al. (2023)	9 weeks	Preacher curl	4 sets x 12RM	50% 60% 70%	↑6.5% ↑7.8% ↑9.7%
Nunes et al. (2020)	10 weeks	Cable preacher curl Barbell preacher curl	3 sets x 8-12RM 3 sets x 8-12RM	50% 50%	↑12.5% ↑12.5%
Costa et al. (2021)	9 weeks	Arm curl	3 sets x 8-12RM	50% 60% 70%	↑7.2% ↑7% ↑9.2%

2.2 Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging is also a non-invasive method with excellent resolution, capable of distinguishing between individual muscles and components. It is often considered the gold standard for assessing regional muscle mass (Smeulders et al., 2010) for example, it can distinguish the clear-cut boundaries among 4 muscles of quadriceps muscle group.

MRI has become just as important as other methods for evaluating body compartments, muscle mass, and related body measurements. Because MRI doesn't use ionizing radiation, it can be safely used for repeated scans in long-term studies (Huber et al. 2020). For volume assessments, a series of two-dimensioned cross-sectional images is taken and combined to calculate the volume. Test-retest reliability for measuring upper and lower body muscles is very high, with intraclass correlation coefficients reaching 0.99 (LeBlanc et al., 2000; Smeulders et al., 2010). However, despite its accuracy in measuring muscle size, MRI is expensive and not widely accessible, so it's less commonly used in research (Huber et al. 2020). Additionally, while MRI is excellent for assessing the area or segmental volume of muscle groups, it does not detect molecular changes within muscle fibers, such as variations in contractile protein concentration or sarcoplasmic protein concentration (Franchi et al. 2018).

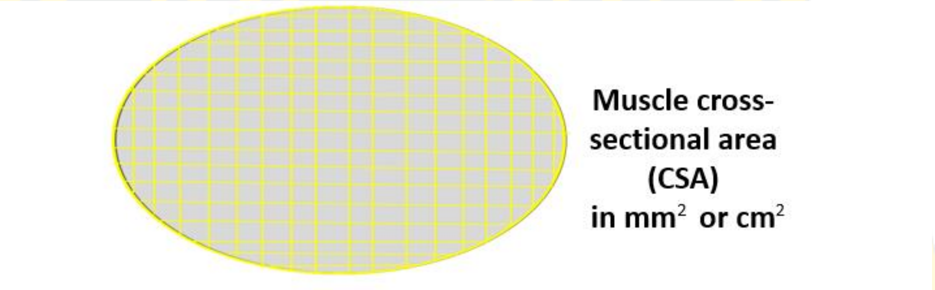


Figure 17. Graphics representing measuring muscle cross-sectional area in square millimeters or square centimeters.

When considering measuring hypertrophic response from resistance training via MRI, the cross-sectional area of muscle is what the researcher is referring to. ***Muscle cross-sectional area is defined as the area within a slice of muscle cut in the transverse plane.*** In previous studies, there were studies that measured muscle cross-sectional area of quadriceps extensors and elbow flexors as well. For example, Seynnes et al. (2007) examine the time-course of early muscular adaptations to high-intensity resistance training. 7 healthy participants were recruited to train with bilateral knee extension exercise for 3 days per week for 5 weeks. Training protocol was 4 sets of 7RM. Muscle cross-sectional area of vastus latearlis were taken at 25% and 50% of femur length. The results demonstrated that muscle cross-sectional area at 25% significantly increased from 22.35 cm^2 to 24.08 cm^2 after training and at 50% significantly increased from 5.21 cm^2 to 5.97 cm^2.

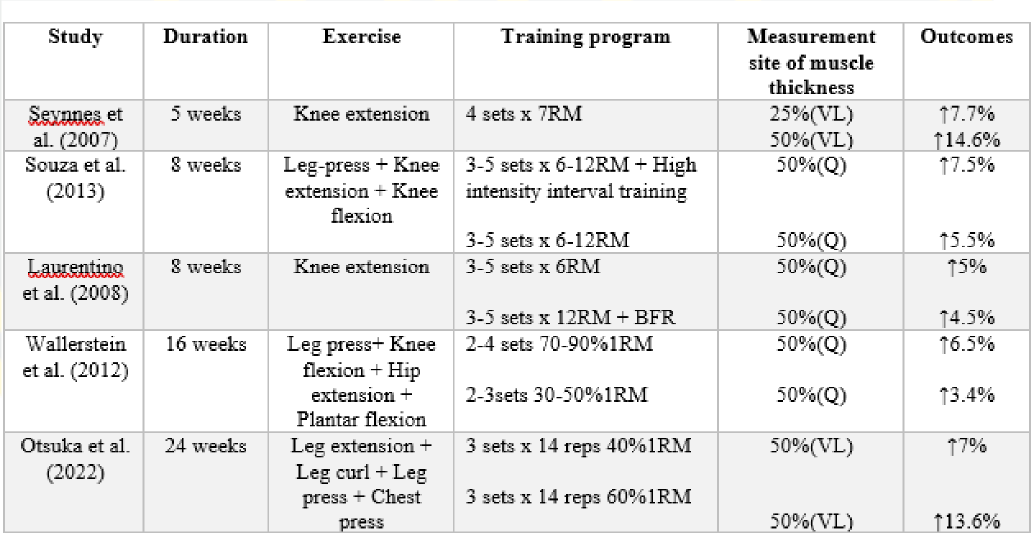
Another study conducted by Souza et al. (2013) was very interesting. They compared concurrent training to strength and interval training on muscle adaptation. Participants in concurrent training group performed leg-press, knee extension, and knee flexion exercises afterwards performing a high-intensity interval training on a treadmill at intensity of 80-100% of maximum speed. After 8 weeks of training, muscle cross-sectional area was measured at 50% of femur length, reported significant increase of quadriceps muscle from 8261.4 mm^2 to 8882.7 mm^2. Similarly, the group that performed strength training only significantly increased muscle cross-sectional from 8215.4 mm^2 to 8668 mm^2

Moreover, Laurentino et al. (2008) investigated the effect of unilateral knee extension training and quadriceps muscle cross-sectional area. In this experiment, the researchers employed with-in subject design with one leg training at high intensity (6RM) and the other leg training at moderate intensity (12RM) with blood flow restriction technique. Muscle cross-sectional area was taken at 50% of femur length. The results demonstrated that muscle cross-sectional area significantly increased in both legs from 75.5 cm^2 to 79.3 cm^2 in high intensity leg and from 86.1 cm^2 to 90 cm^2 in moderate intensity leg.

In the older participants, MRI was possible method of measurement as well. Wallerstein et al. (2012) examined effects of series of exercises such as Leg press, Knee flexion, Hip extension, and Plantar flexion on muscle cross-sectional area of quadriceps muscle. One group of older participants performed heavy training at 70-90%1RM while the other group use lighter load but with more explosive movement at 30-50%1RM. Results demonstrated that regardless of the methods of training, both groups significantly increased muscle cross-sectional area of quadriceps muscle: from about 4700 mm^2 to 5000 mm^2 in ST and from about 4300 mm^2 to 4440 mm^2.

Another recent study that investigated change in vastus lateralis cross-sectional area was conducted by Otsuka et al. (2022). Fifty participants completed the 24 weeks of exercise intervention and had their vastus lateralis muscle measured via MRI at 50% of femur length. Resistance training included machine training: leg extension, leg curl, leg press, and chest press. The training weight was 40%1RM in the low intensity group and 60%1RM in the moderate intensity group. The findings showed that vastus lateralis cross-sectional area increased significantly in both group: from 17.1 cm^2 to 18.3 cm^2 and 17.7 cm^2 to 20.1 cm^2 in low and moderate intensity groups, respectively.

Table 3. Previous studies which employed MRI to measure muscle cross-sectional area of quadriceps muscle



Study	Duration	Exercise	Training program	Measurement site of muscle thickness	Outcomes
Seynnes et al. (2007)	5 weeks	Knee extension	4 sets x 7RM	25%(VL) 50%(VL)	↑7.7% ↑14.6%
Souza et al. (2013)	8 weeks	Leg-press + Knee extension + Knee flexion	3-5 sets x 6-12RM + High intensity interval training 3-5 sets x 6-12RM	50%(Q) 50%(Q)	↑7.5% ↑5.5%
Laurentino et al. (2008)	8 weeks	Knee extension	3-5 sets x 6RM 3-5 sets x 12RM + BFR	50%(Q) 50%(Q)	↑5% ↑4.5%
Wallerstein et al. (2012)	16 weeks	Leg press+ Knee flexion + Hip extension + Plantar flexion	2-4 sets 70-90%1RM 2-3sets 30-50%1RM	50%(Q) 50%(Q)	↑6.5% ↑3.4%
Otsuka et al. (2022)	24 weeks	Leg extension + Leg curl + Leg press + Chest press	3 sets x 14 reps 40%1RM 3 sets x 14 reps 60%1RM	50%(VL) 50%(VL)	↑7% ↑13.6%

3.Mechanisms of muscle strength

Strength adaptation occurs at the very fast rate compared to muscle hypertrophy (MacDougall & Sale 2014). For hypertrophy to be occurred and obviously observed, it may take at least or more than 6 weeks or 18 sessions of progressive resistance training (Damas et al. 2018). In one classic study of Hickson (1980), it was the very early study to show that after only 1 week of legs strength training that including various legs exercises such as parallel squat, knee flexion, knee extension, leg press, and calf raise, muscle strength as qualified by 1RM parallel squat significantly improved from baseline. Besides, the gain progressively continuously increased until the 10 weeks of training. The average total increment of strength was about 42kg or 44% above baseline. Literature has been well-documented that both physical and neural adaptations play the important roles in increasing strength gains (Sale 2003). Numbers of studies that reported increased muscle hypertrophy usually accompanied the finding by the increase in muscle strength as well. For example, Schoenfeld et al. (2015) found that after strength training at low intensity, 30RM squat, for 8 weeks, the adaptations resulted in both significant improvement in muscle hypertrophy of quadriceps muscle (9.5%, $p<0.05$) and muscle strength (+8.8%, $p<0.05$). Moreover, when resistance training was conducted at high intensity, 10RM squat, the level of muscle hypertrophy was not significantly different (+9.3%, $p<0.05$) from low intensity; nevertheless, the level of strength gain significantly increased up to +19.6% ($p<0.01$), showing statistically different from low intensity training ($p<0.05$). The results of this study suggested that when it came to maximize muscle strength, the implementation of high intensity program was more beneficial over the chronic adaptation when the training duration was equated. Furthermore, in part of adaptation, strength gain was not solely depending on muscle size. According to Sale (1988), in the early training state by which muscle size was not observed, muscle strength could significantly increase to the certain degree. This was theoretically contributed to the neural adaptation. Physiologically, there were three distinct neural adaptations that subsequently contributed to strength gain of agonist muscle: increase in motor unit recruitment, and increase in motor unit firing rate, and increase in rate of force development (Sale 1988). The details of these adaptations were as follow.

3.1 Increase in agonist activation

From physiological adaptation standpoints, there were three primary mechanisms by which the adjustments in neural adaptation could result in the increase activation of agonist muscle. The first one is to increase the degree of motor unit recruitments; the second one is to increase the motor unit firing rates; the third one is to increase the rate of force development.

3.1.1 The increased degree of motor unit recruitment

Skeletal muscle is composed of many thousands of heterogeneous single muscle fiber in many bundles of fascicles. A single muscle fiber can have specific characteristics on its shortening velocity and maximal force generating capability. In general, when classified by these characteristics, there are two main types of muscle fibers: Type l or slow-twist fiber and Type ll or fast-twist fiber. Generally, type l or slow-twist fiber will have the slow shortening velocity and can produce low force while type ll or fast-twist fiber will have the fast shortening velocity and can produce higher force (Kenny, Wilmore, & Costill, 2020). Scott et al. (2001) explained that the myosin ATPase hydrolysis in fast-twist fiber is greater 2 to 3 times than that of slow-twist fiber. As a result, fast-twist fiber can make the repeated cross-bridge cycles at faster rate than slow-twist fiber. Type ll fibers are technically specific to type lla and type llx. The difference between type lla and type llx lies mainly in its fatigue resistance and oxidative capacity (MacDougall & Sale 2014). The highest to lowest fatigue resistance ranges from type l, type lla, and type llx, respectively (Krap 2001).

Motor unit is how the brain governs the skeletal muscle fibers. The central nervous system controls the activation of muscle fibers through the activation of the motor units. The finite numbers of muscle fibers belong to a single motor unit. Some motor units control tens to thousands of muscle fibers. Heckman and Enoka (2004) reported that in the small muscles at hand, the number of muscle fibers vary from 10 to 1800 muscle fibers per a single motor unit while the big muscles such as tibialis anterior contain from 50 to 12000 muscle fibers per a single motor unit. The average number of muscle fiber per a motor unit is called the innervation ratio (MacDougall & Sale 2014). According to MacDougall and Sale (2014), the motor unit itself can be divided into 1) slow, fatigue-resistant motor unit, 2) fast, fatigue-resistant motor unit, and 3) fast, fatigable motor unit. The number of muscles fiber per motor unit also varies. Slow, fatigue-resistant or type l motor unit usually contains less than or equal 300 muscle fibers while the fast, fatigable and fast, fatigue-resistant or type ll motor units usually innervate at least more than 300 muscle fibers (Kenny, Wilmore, & Costill, 2020). Besides, the activation of the motor unit is called the motor unit recruitment which must follow the rule of Henneman's size principle (Brown 2017). According to Henneman's size principle, the smallest motor unit, which usually innervates small numbers of muscle fibers and most type l fibers, will be recruited first. However, the force production from these small motor units is comparatively low. Afterwards, when the more force demands are placed on the muscle, the larger motor units which are fast, fatigue-resistant and fast, fatigable and usually innervating type ll fibers will be progressively recruited later on to support the force production (Brown 2017).

At the beginning of resistance training, untrained subjects usually do not reach the maximal recruitments of the motor unit pool. As a result, huge numbers of muscle fibers that mostly belong to high threshold motor units are left out of use. When the resistance exercise continues and the intensity progressively increases, the magnitude of required force becomes higher for a given task. The central command is then responsible to recruit the fast, fatigue-resistant motor units and the fast, fatigable motor units to in addition to the already used slow fatigue resistance motor units to compensate the required force (Suchomel et al. 2018). The percentage of maximum force that motor units are recruited is referred as "recruitment threshold". Low threshold motor units which are mostly governing type l fibers while recruited produce low force while high threshold motor units which are mostly governing type lla and type llx fiber while recruited produce high force (MacDougall & Sale 2014). The study of Enoka and Fuglevand (2001) had showed that in triceps brachii muscle, about 20% of total muscle fibers were controlled by small amount of high threshold motor units, fast fatigable, in which accounted for only 5% of total number of motor units. While more than 75% of total motor units are low threshold motor units, the numbers of fibers they controlled, however, accounted for only about 30%. So, when untrained subjects are able to recruit higher threshold motor units, after certain period of experiencing progressive resistance training such as weightlifting, the substantial increase in muscle strength exhibits (Suchomel et al. 2018).

3.1.2 The increased motor unit firing rates

Motor unit firing rates are sometimes referred as discharge rate of rate coding (MacDougall & Sale 2014). According to the force-frequency relationship, motor units can be activated with a range of frequency. At high frequency of activations by increasing the firing rates, muscle force can be increase up 1000-1500% (Sale 1988; Suchomel et al. 2018). According to Kenny, Wilmore, and Costill (2020), it was suggested that slow controlled tempo resistance training has limited evidence to show to increase firing rates. Rapid movement or ballisctic-type instead appears to be more suitable to be particular stimulus for increasing motor unit firing rate. Training strategies that can increase the motor unit firing rates such as explosive/power training associating with intense brief explosive of high frequency of all motor units might be preferable. For example, Kamen and Knight (2004) evaluated changes in motor unit firing rates in young and older adults during exercise resistance training. 8 young, average age 21 years old, and 7 older adults, average age 77 years old, were recruited to the study. The training exercise included 3 times per week for 6 weeks of 10 sets of knee extension exercise at intensity 85%1RM with maximal effort. The testing of firing rates was to perform 5 seconds of maximal voluntary isometric knee extension at knee flexion of 110 degree. After 6 weeks of training, the results showed that the maximal force increased in young adults for average 16% and 10% for old adults. Besides, the motor unit firing rates at different intensity were reported to increase in both young and older adults. For example, the results showed that pre-training (day 1) firing rates were about 25 impulses per second at 100%MVC in young adults and the post-training (day 50) firing rates improved up to about 28 impulses per second at 100%MVC. The similar increase in firing rates was also observed in older adults as well, from about 18 impulses per second at 100%MVC to about 27 impulses per second at 100%MVC.

3.1.3 The increase of rate of force development

The consequence of training-induced improvement in motor unit firing rate will finally result in the increase in rate of force development (MacDougall & Sale 2014). Rate of force development refers to the time by which is spent to develop force (Aagaard, 2002) Athlete with higher rate of force development can produce high force at high velocity and rate of force development also has been showed in sport-science literature to be correlated with many sport performance such as sprinting (Slawinski et al. 2010), jumping (McLellan et al. 2011), and weight lifting (Kawamori et al. 2006).

From physiological standpoint, when athlete can produce higher motor unit firing rates at the early very short period of time, such as less than 250 milliseconds (Turner & Jeffreys 2010), higher force is developed within this short period of time. In many sports that require higher force with limited time, rate of force development can be a determinant of winning or losing in competition. For example, during sprinting with very short period of time for ground contraction, athlete must produce the very high force to move forwards during each stride. The stretch-shorting cycle during sprinting is only about 80-90 milliseconds which is classified as the very fast stretch-shorting cycle movement (Taylor & Beneke 2012). Therefore, athletes with higher rate of force development could be able to stride more powerfully sending themselves forwards further that those with low rate of force development. Study has been reported that adaptation from strength training such as increased tendon stiffness can contribute to the better rate of force development because stiff tendon can transfer force quicker to bone and induce the movement (MacDougall & Sale 2014). Heavy resistance training was one of the most popular techniques to improve tendon stiffness. For example, Kubo et al. (2006) found that high intensity at 80%1RM in knee extension exercise significantly increase tendon stiffness by 30% after 12 weeks of training.

Besides, fast explosive intent of movement seems to affect the adaptation of rate of force development as well. As showed in the study by Andersen et al. (2010). The group of researchers investigated the effect of 14weeks resistance training and adaptation in rate of force development at early phase (<100ms) and at late phase (>200ms). Although, the resistance training program included many commonly used exercises such as leg press, hack squat, knee extension, and hamstring curl, the researcher confined that the participants were instructed to contract the muscle the controlled slow manner in order to avoid injuries from training. After 14 weeks of training, it was showed that the late phase of rate of force development (>200ms) increased to 11% from baseline value ($p<0.05$); however, the early rate of force development was not improved. Besides, the early (up to 140ms) rate of force development significantly decreased by 10-18% ($p<0.05$) from baseline value. This decrease was clearly detrimental for sport that relied on early rate of force development.

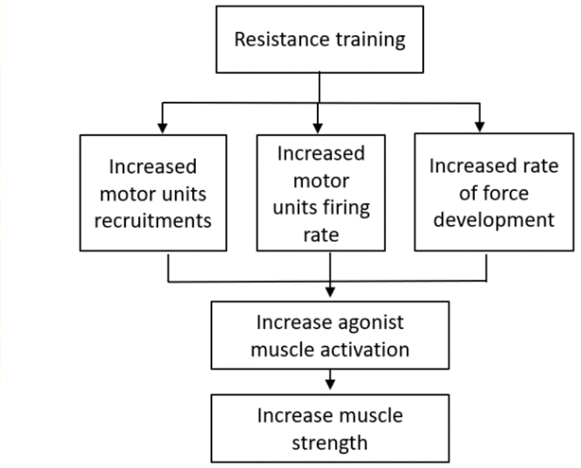


Figure 18.Mechanism of increased muscle strength.

4. Physiology of blood flow restriction resistance training

In practice, ***blood flow restriction (BFR) training involves applying pressurized cuffs or elastic bands to the most proximal portion of the upper or lower limbs during exercise*** (Patterson et al. 2019). This technique can be applied across various exercise modalities, as demonstrated in the literature, including aerobic exercises like walking (e.g., Kim et al. 2016) and cycling (e.g., Abe et al. 2006), anaerobic exercises such as resistance training (e.g., Fahs et al. 2015) and sprint training (e.g., Behringer et al. 2017), and even water-based training (e.g., Araujo et al. 2015). ***The primary mechanism behind BFR is the external pressure applied to the working muscle, which occludes venous outflow and partially restricts arterial inflow*** (Manini & Clark 2009). This process can lead to various acute and chronic physiological adaptations following a period of training (e.g., Davids et al. 2021; Chua et al. 2022).

Since its introduction in the 1990s, the BFR technique has garnered significant interest from researchers. Numerous studies have been conducted to explore its effects on various performance and health variables, including ***100-meter dash time*** (e.g., Behringer et al. 2017), ***power output*** (e.g., Wilk et al. 2020), ***one-repetition maximum strength*** (e.g., Luebbers et al. 2019), ***time to exhaustion*** (e.g., Paton et al. 2017), ***30-second sit-to-stand test*** or ***6-minute walk test*** (Clarkson et al. 2017), and ***muscular thickness*** (e.g., Laurentino et al. 2022). These studies have been conducted across both male and female participants (Count et al. 2018) and in both general and special populations (Perera et al. 2022).

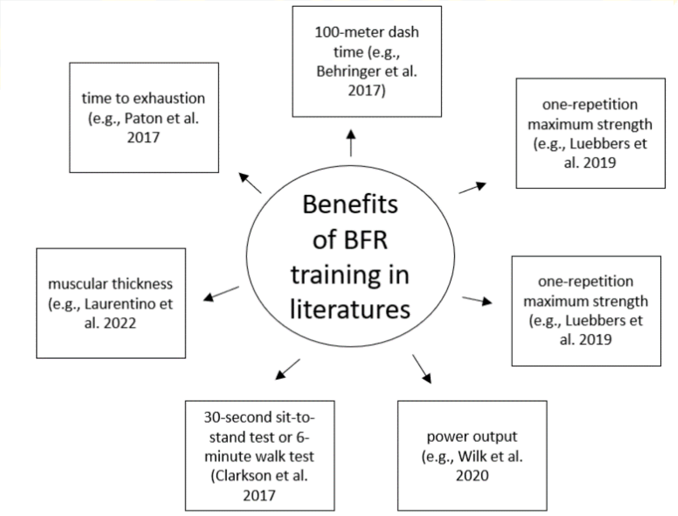


Figure 19. Literature of effectiveness of blood flow restriction training.

From a physiological perspective, ***when BFR is not applied***, the working muscle, such as the quadriceps during squatting, receives an increased volume of blood via femoral arterial inflow, leading to greater muscle perfusion and an acute increase in muscle volume due to blood perfusion. (Kenny, Wilmore, & Costill, 2020). During dynamic muscle contractions, the muscle pump initially enhances venous return by rhythmically contracting and relaxing, which squeezes the veins and helps pump more blood back to the heart. However, as arterial blood flow increases and the muscle fills with blood, the resulting intramuscular pressure from both the contraction and blood pooling can compress the veins, restricting venous return and causing blood to accumulate within the muscle (MacDougall & Sale 2014). This restriction leads to the build-up of metabolic byproducts such as lactate and hydrogen ions, resulting in reduced blood pH, increased perceived pain, heat accumulation, and a decrease in action potentials along the sarcolemma (Phillips 2015). Eventually, this leads to momentary muscular failure, where the muscle can no longer sustain the contraction and the exercise must be terminated.

In contrast, ***when BFR is applied***, at the proximal portion of a working muscle such as the top of the biceps brachii during an elbow flexion exercise, the external cuff exerts pressure on the artery (e.g., the brachial artery) and the surrounding tissue. Physiologically, ***applying BFR during an elbow flexion exercise reduces blood flow*** from the brachial artery to the biceps brachii muscle, ***decreasing oxygen delivery***. This leads to a rapid decline in muscle oxygenation during just a few contractions, ***causing significant local fatigue to occur sooner than it would without BFR*** (Jessee et al. 2018). The reduced oxygenation ***shifts energy production to glycolytic pathways***, ***increasing the accumulation of metabolic byproducts like lactate*** (Phillips 2014). ***Additionally, the cuff pressure compresses the deep brachial vein, blocking venous outflow and causing blood to pool in the muscle, further enhancing metabolite accumulation*** (Jessee et al. 2018). ***Both metabolite accumulation and local fatigue are crucial for inducing muscle hypertrophy because they can stimulate the recruitment of***

additional motor units, particularly those controlling fast-twitch fibers, which have the greatest potential for growth (Schoenfeld 2022). Fast-twitch fibers need to be activated during exercise to maximize hypertrophic response (Fry 2004).

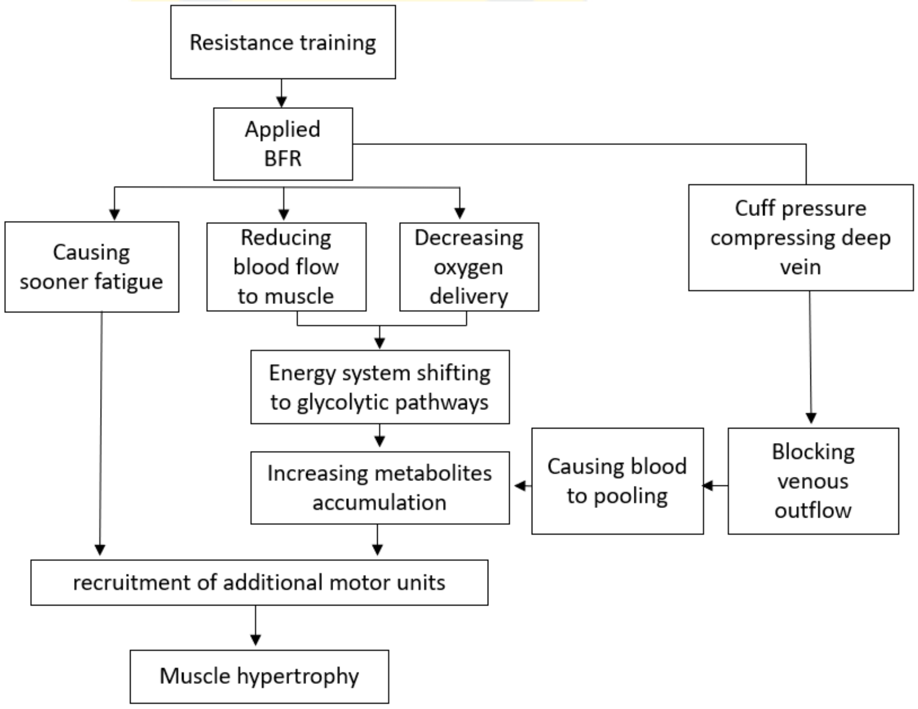


Figure 20. Physiological response of blood flow restriction training to muscle hypertrophy.

Moreover, the metabolic stress from hypoxic conditions, such as increased lactate and nitric oxide, can stimulate anabolic hormones like human growth hormone, IGF-1, and testosterone (Godfrey et al. 2003; Schoenfeld 2013). For example, Takarada et al. (2000) examined the hormonal response to low-intensity resistance training with BFR in healthy young men. The study applied pressurized cuffs at approximately 210 mmHg around the proximal thighs during knee extension exercises at 20% 1RM for five sets to failure, with 30 seconds of rest between sets. Post-exercise blood samples revealed a significant increase in plasma lactate and growth hormone concentrations, with growth hormone levels rising up to 290 times the baseline

(Takarada et al. 2000). Similarly, Sato et al. (2005) compared the growth hormone responses between arm and leg exercises with BFR. Participants performed biceps curls, triceps press-downs, squats, and leg curls at 20% 1RM with cuffs set at 50% above systolic blood pressure. The 30-15-15-15 repetition scheme with 30 seconds of rest resulted in significantly elevated lactate and growth hormone levels post-exercise ($p<0.001$). Lactate levels reached approximately 10 mmol/l immediately post-exercise, while growth hormone peaked at 25 ng/ml for arm training and 30 ng/ml for leg training at 15 minutes post-exercise.

Another potential that ***blood flow restriction might facilitate muscle hypertrophy was inducing satellite cells activity*** (Pearson & Hussain 2014). Satellite cell is a muscle-specific stem cells locating under the basal lamina of muscle fibers and the main function of these stem cells is responsible for muscle repair and regeneration (Kenny, Wilmore, & Costill, 2020). More specifically, when the muscle fiber is damaged, the satellite cell will be activated from quiescent state. If the degree of micro-damage is minor, the satellite cell will get through proliferation – increasing in numbers, differentiation – moving to the damaged site, and fusion – fusing to the muscle fiber to help in the repair process (Brown 2017).

The necessary role of satellite cell in muscle hypertrophy was firstly demonstrated in the early study showing that after 10 weeks of RT, ***the hypertrophied muscle was accompanied by increase number of satellite cell and myonuclei within muscle*** (Kadi & Thornell 2000). The researcher assigned 9 healthy women to RT program including shoulder press, rowing, triceps pulldown, and latissimus pulldown at intensity 10-12 repetition maximum, 3 times a week for 10 weeks. After training, they found that the significant 36% increase in trapezius muscle cross-sectional area was observed ($p=0.005$). Together with increased fiber size, the significant increase in the numbers of myonuclei per fiber and numbers of satellite cells were also observed (+70%, $p=0.007$ and +46% $p=0.01$, respectively). The researchers suggested that ***it appeared***

necessary for the acquisition of additional myonuclei to support the enlargement of multinucleated muscle to hypertrophy after 10 weeks of RT (Kadi & Thornell 2000). Schoenfeld (2020) proposed that during high intensity training such as RT that causes micro-damage to higher degree on muscle fibers, ***the satellite cells often act through the process of donation – managing to donate a new myonucleus to the existing fiber***. As a result, the numbers of myonuclei per fiber increase.

Brown (2017) suggested that the number of myonuclei in muscle fibers is directly related to muscle protein synthesis, influencing muscle hypertrophy and strength. In simpler terms, the extent of muscle hypertrophy depends on the number of myonuclei within the muscle. ***This implies that myonuclei might be a limiting factor in muscle adaptation following resistance training*** (Robert et al. 2018). Robert et al. (2018) compared high and low responders to resistance training-induced hypertrophy and found that high responders exhibited greater hypertrophy, possibly due to a more significant increase in satellite cell numbers and fusion potential. Supporting this, Bellamy et al. (2014) observed that participants with the greatest increase in myonuclei 72 hours after the first training session experienced the most substantial muscle hypertrophy over 16 weeks. In their study, 23 untrained males underwent a resistance training protocol that included exercises like chest press and leg press, progressing from 2 sets at 70% 1RM to 4 sets at 85% 1RM. After 16 weeks, participants showed a 7.9% increase in quadriceps volume and a 21% increase in myofiber cross-sectional area. Additionally, satellite cell counts in type I and type II fibers increased significantly (from 10.7 to 12.1 cells/type I fiber, $p<0.05$; and from 11.3 to 13 cells/type II fiber, $p<0.05$). Significant correlations were found between changes in satellite cell numbers and quadriceps volume changes ($p=0.012$ and $p=0.027$, respectively). These findings highlight the critical role of satellite cells in muscle hypertrophy induced by RT (Bellamy et al. 2014).

In human study of blood flow restriction, low intensity vibration with blood flow restriction had also shown to increase the acute activation satellite cells in only one bout (Aguayo et al. 2016). Aguayo et al. (2016) compared the two vibration protocols: whole-body vibration during static half squat with and without blood flow restriction at 200mmHg pressure during exercise. The exercise was performed for 4minutes each set and for total 3 set with 3 minutes resting interval. The results showed that when compared to whole-body vibration without blood flow restriction, the satellite cell quantity significantly increased in vibration with blood flow restriction (p=0.002); furthermore, when expressed according to fiber type, satellite cell quantity increased in the vibration with blood flow restriction group only (p=0.016 and p=0.002 for type I and type II myofibers, respectively) (Aguayo et al. 2016). This difference might be explained by the restriction of blood flow creating higher extent of intramuscular metabolic stress such as low level of muscle oxygen and more lactate production within the working quadriceps muscle during maintaining half squat vibration. It was potential that these metabolic stresses might augment the tension created in the muscle.

Another study by Wernbom et al. (2013) also found that similar results that blood flow restriction resistance training could increase the numbers of satellite cells in human skeletal muscle. Wernbom et al. (2013) investigated signaling pathway after a single bout of low intensity resistance training with and without blood flow restriction. Six males and one females were randomly assigned to train one leg with partial blood flow restriction and the other leg to exercise without blood flow restriction. In order to match the numbers of repetition between legs, the leg with blood flow restriction was performed first because high level of fatigue made the failure point to be reached earlier. The exercise included unilateral knee extension at 30%1RM to repetition failure for total 5sets. The cuff pressure was set at 90-100mmHg, wrapped around the proximal part of the thigh and kept inflated throughout the exercise period. The results demonstrated that the number of satellite cells significantly increased at 1 hour post exercise in leg training with blood flow restriction (+33.1, $p<0.05$). However, in leg training with free blood flow, the percentage of satellite cells did not significantly change at any measured time-point ($p>0.05$).

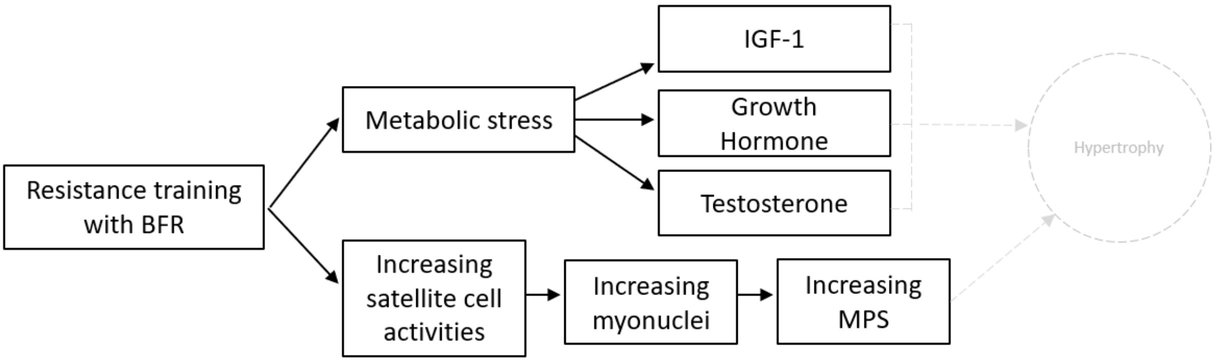


Figure *21*.Resistance training with blood flow restriction increased metabolic stress, stimulating anabolic hormone response and satellite cells activities.

Nevertheless, the mechanism by which the blood flow restriction elicited myofiber satellite cells was still unclear. ***The local hypoxia might play a significant role in inducing satellite cell activities.*** Bjornsen et al. (2021) recently compared resistance training with blood flow restriction on leg extension machine at intensity 20%1RM. Eighteen untrained healthy men was assigned one leg to training to repetition failure while the other leg to training to non-failure. The non-failure training leg performed 30 repetitions for the first set, and 15 repetitions for the next 3 sets while the failure training leg performed 4 sets of as many repetitions as possible. 14 training sessions were distributed over 2 five-day blocks interval by ten-day rest. The results demonstrated that the muscle thickness of rectus femoris and vastus lateralis muscles of both training legs significantly increased around 4-10% above baseline level ($p<0.01$) while the thickness of vastus intermedius muscle remained unchanged ($p>0.05$). The numbers of satellite cells significantly increased at 10days post intervention in both type l (92-134%, $p<0.05$) and type ll fiber (23-48%, $p<0.05$). The authors also reported significant increase in myonuclei numbers in both conditioning legs. The numbers of myonuclei in type l fibers increased from baseline to 11.7% ($p=0.01$) and 17% ($p<0.01$) in non-failure leg and failure leg, respectively. The numbers of myonuclei in type ll fibers increased from baseline to 11.2% ($p<0.01$) and 19.9% ($p<0.01$) in non-failure leg and failure leg, respectively. ***Using resistance training with blood flow restriction and training to repetition failure in every set may increase local muscle fatigue and metabolic stress. This heightened hypoxia-induced metabolic stress could enhance satellite cell activation and myonuclei addition, as evidenced by a greater increase in myonuclei.***

Moreover, hypoxia is induced by blood flow restriction can cause post-exercise reperfusion which it was hypothesized that muscle reperfusion after the short period of ischemic preconditioning might enhance muscle protein synthesis and prevent muscle protein breakdown as showed by studies demonstrating that intermittent application of blood flow restriction even without exercising could offset muscle mass and strength loss during immobilization period (Takarada et al. 2000; Kubota et al. 2008). In a study by Tanimoto et al. (2005), they found that the after finishing exercise with blood flow restriction, the mean level of maximal muscle oxygenation significantly increased up to 143% compared to baseline. ***This higher extent of oxygen in muscle indicated the higher extent of blood reperfusion after blood flow restriction training.*** In the previous study Takarada et al. (2000) investigated the effect of blood flow restriction technique at approximately 240mmHg for 5 minutes, interval by 3 minutes rest for 5 times, in patients who underwent operation of knee ligaments and found that without occlusive stimulus, the quadriceps and hamstrings muscle cross-sectional area decreased by 20% and 11%, significantly higher ($p<0.05$) compared to occlusive stimulus (9% and 9%, respectively). The mechanism by which the reperfusion might reduce muscle loss was claimed that the accumulation of metabolites and low level of muscle oxygenation during blood flow restriction caused the intracellular swelling which was believed to endanger to structural integrity of cell membrane. As a result, ***the reperfusion-induced swelling might promote muscle protein synthesis and decrease muscle protein breakdown*** (Schoenfeld 2013). Furthermore, cell swelling was also potentially associated with satellite cell function as shown by the previous study. The researcher found that dietary supplementation, Creatine monohydrate, which was well-known to induce cellular hydration could increases satellite cell proliferation and fusion which might regulate long-term skeletal muscle hypertrophy (Dangott et al. 2000). However, the underlying mechanisms of anabolism of cell swelling have yet to be fully determined; therefore, more studies are needed to be confirming this mechanism.

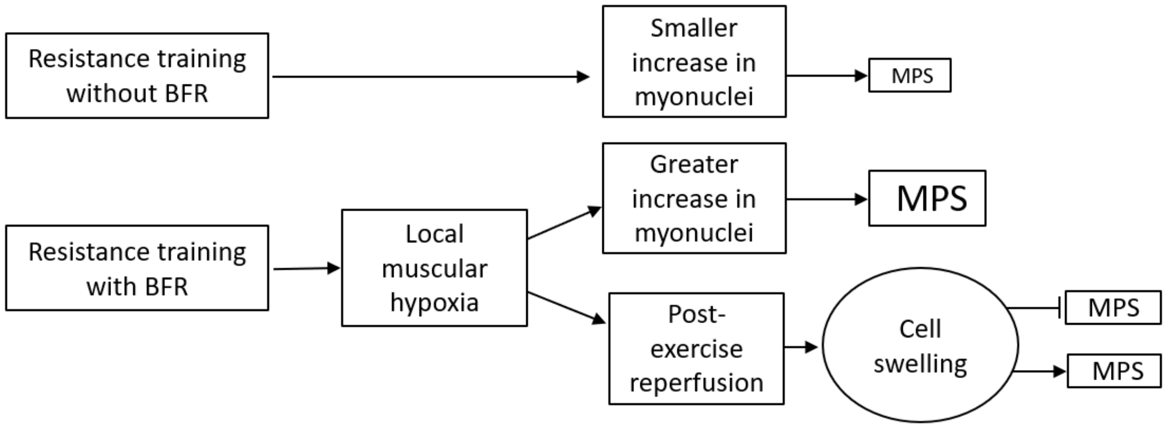


Figure 22. Utilizing resistance training with BFR causing increase greater numbers of myonuclei and post-exercise reperfusion causing cell swelling.

Last but not least, ***the latest possible mechanism that blood flow restriction might enhance muscle hypertrophy was through the increment of formation and development of new capillary network to parts of the body***. Recent study by Thomas et al. (2022) had found that short-term doing of aerobic exercise before start resistance training could augment the degree of muscle hypertrophy in both healthy young men and women. In this study 14 young participants entered the program of 6 weeks aerobic exercise of one leg cycling, 45 minutes for 3 times per week at approximately 80-90 revolutions per minute and followed by 70-80%1RM resistance training consisting of bilateral squats, leg press, leg extension, hamstring curls, and calf raises, 3 sets of 10-12reps per set per exercise for 10 weeks. After training muscle hypertrophy and muscle capillary were observed to examine the differences between legs with and without aerobic training. The results demonstrated that type 1 fiber capillary to fiber perimeter exchange ratio significantly increased from baseline (4.9 per 1000µm) to post aerobic training in aerobic-training legs (7.0 per 1000µm, $p<0.0001$) but not in non-aerobic-training legs (5.1 per 1000µm, $p>0.05$). Besides, in type ll fiber, the capillary to fiber perimeter exchange ratio also significantly increased from baseline (4.6 per 1000µm) to post aerobic training (5.6 per 1000µm, $p<0.05$) only in aerobic-training legs. No significant increase in non-aerobic-training leg was observed. When it came to muscle fiber cross-sectional area, the analysis of muscle biopsy of vastus lateralis muscle showed that aerobic-training legs increased both type l (+19%, $p<0.05$) and type ll (+40%, $p<0.05$) fiber cross-sectional area, while non-aerobic-training legs only increased in type ll fiber cross-sectional area (+13%, $p=0.05$). The authors of this study proposed that the ***increase in capillarization after aerobic training would increase satellite cell activation*** that would affect the remodeling process of muscle fibers, supporting the hypothesis that muscle capillarization might be a critical factor to support hypertrophic adaptation (Thomas et al. 2022).

Therefore, training program for maximizing muscle hypertrophy should include protocol that maximizing muscle capillarization as well. Besides, due to the nature of high numbers of repetitions and low intensity of blood flow restriction resistance training, this method of training might enhance muscle fiber capillarization which in turn would affect hypertrophy in long term adaptation. For example, Evans et al. (2010) had found investigated the short-term effect of low intensity resistance training with blood flow restriction in 9 healthy recreationally active men. The exercise program included 4 weeks of calf muscle low intensity resistance training, 4 sets of 50 repetitions for each set. The intensity of training was equal to 10-15% of body mass. The within subject research design was employed that one training leg was applied with blood flow restriction and the other leg was not. Calf muscle blood flow was measured before and after short-term training ended. The showed that before the experiment, there was no significant difference between legs in calf blood flow in blood flow restriction and non-restriction legs (3.64 vs 4.02ml/min, respectively); afterwards calf muscle blood flow significantly increased by 26% in the restricted leg (4.56ml/min, $p<0.05$) but did not significantly increase in the unrestricted leg ($p=0.06$). It had been hypothesized that metabolic stress that occurred during blood flow restriction might play the important role inducing muscle hypertrophy as well as the ***metabolic stress-induced hypoxia might also enhance muscle capillary network expanding which in turn possible affected long-term muscle adaptation*** (Hudlicka & Brown 2009).

Moreover, in the most recent systematic review of the physiological determiners differentiating between high responders and low responders suggested that capillary network might be the limiting factors that determined how much a person could hypertrophy after training (Roberts et al. 2018). The researchers demonstrated through the existing literature that it was possible that high responders to hypertrophic training would have more capillary in muscle fiber than low responders. In the study of Snijders et al. (2017), it was found that the older adults who entered resistance training program for 24 weeks experienced the significant increase in muscle mass; however, those who had higher baseline capillary density experienced greater increase in type ll fiber cross-sectional area. Therefore, it was potential that capillary content or enhanced endothelial function might regulate muscle hypertrophic adaptation. Besides, due to ***the fact that blood flow restriction training substantially induced metabolic stress and hypoxia as well as many growth factors, such as HIF-1alpha and vascular endothelial growth factors, related to capillarization to higher degree than traditional resistance training alone***, these mechanisms might augment muscle hypertrophy after long-term resistance training if blood flow restriction was combined.

4.1 Hypertrophic effect of low intensity resistance training with blood flow restriction compared to high intensity resistance training alone

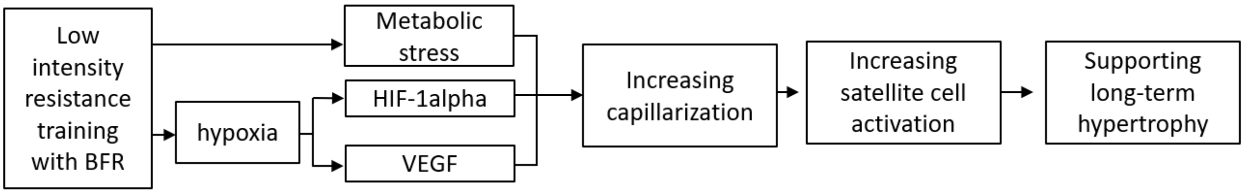


Figure 23.Increasing capillarization from BFR supports long-term muscle hypertrophy.

If we look at the recommendation of many renowned associations about resistance training such as American College of Sports Medicine, National Strength and Conditioning Association, or National Academy of Sports Medicine, they tend to do agree upon the training intensity that should be used to elicit muscle hypertrophy.

For example, according to the recommendation of ***NSCA***, it is suggested that the appropriate intensity for resistance training to elicit muscle hypertrophic response is around 67-85%1RM for 6-12 repetitions and 3-6sets (Brown 2017).

In the same way, according to ***ACSM***, for the novice and intermediate individuals, it is suggested training at moderate to heavy intensity the intensity of 70-85%1RM for 1 to 3 sets of 8-12 repetitions per exercise, and for the advanced individuals suggested training at 70-100%1RM for 3 to 6 sets of 1-12 repetitions per exercise (Ratamess et al. 2009).

Similarly, ***NASM*** recommends high volume, moderate to high intensity and moderate or low repetitions (6–12RM) for muscle hypertrophy goal. The consensus about hypertrophy training tends to end up that one should train at the intensity of moderate to heavy external load for this purpose (Clark et al. 2012).

However, when low intensity resistance training is combined with blood flow restriction technique, numbers of studies have demonstrated that the hypertrophic effect of RT is similar to those training according to the recommendation or at moderate to high intensity (e.g. Yasuda et al. 2011; Vechin et al. 2015; Lixandrao et al. 2015; Libardi et al. 2015).

For Instance, the very early study by Kobu et al. (2006) comparing the effects of low intensity resistance training with blood flow restriction on muscle and tendon properties with high load resistance training. This study was interesting in physiological aspect because it was documented that in order for tendon to adapt, the accumulation of high tension and workload were required and took period of time. Therefore, whether or not low intensity resistance training with blood flow restriction would substitute the same adaptation brought by heavy resistance training with high tension was always the topic of interest. The researchers employed the with-in subject design on 9 healthy young men, average age 25 years old. One training leg was assigned to low intensity resistance training with blood flow restriction, 20%1RM 4sets of 25,18,15,12 repetitions, respectively with 30 second rest. The other leg was training at high intensity, 80%1RM 4sets of 10repetitions with 1 minute rest. The 1RM and load assignment were measured and readjusted every 4 weeks. The cuff pressure was gradually increased throughout the training weeks from around 180 to 240mmHg. Knee extension machine was used for experiment. After 12 weeks of training, the cross-sectional area of rectus femoris muscle was measured via MRI and the results demonstrated that both training legs significantly increased muscle cross-sectional area (5.9%, $p=0.022$ vs 7.4%, $p=0.016$ for low and high intensity training leg, respectively). The anatomical measurement of fascicle angle of vastus lateralis muscle also increased to the similar extent between legs (6.1%, $p=0.024$ vs 7.5%, $p=0.021$, respectively). For tendon adaptation, the results showed that no significant changes were observed in the patella tendon cross-sectional area in both training legs. The possible explanation might be that the period of experiment was too shot for the accumulated tension to affect tendon hypertrophy.

In 2012, Laurentino et al. conducted a study to determine change in muscle strength and hypertrophy and association with Myostatin gene expression after resistance training. 29 healthy active men, age 20-23 years old, were participated in this study, randomly allocated to low intensity resistance training (20%1RM), low intensity resistance training with moderate blood flow restriction, and high intensity (80%1RM). All of the groups underwent 8 weeks resistance training program including bilateral knee extensions for 3-4 sets with 1 minute rest. Low intensity groups performed 15 repetitions and high intensity group performed 8 repetitions each set. The cuff pressure of 50% of arterial occlusion pressure (average at 94.8mmHg) was applied throughout the training protocol. After 8 weeks of training, quadriceps muscle cross-sectional area was measured via MRI, showing the significant increases in low intensity resistance training with blood flow restriction and high intensity groups (6.3%, $p=0.0007$ and 6.1%, $p=0.0004$, respectively). However, no significant change was observed in low intensity without blood flow restriction group (2.0%, $p=0.9653$).

Besides, the Myostatin gene expression showed significant reduction in blood flow restriction and high intensity groups (45%, $p<0.0001$ and 41%, $p=0.0004$, respectively). The degree of reduction was not different between groups at post-test ($p=0.99$). Physiologically, Myostatin is a myokine that functions as catabolism, increasing the muscle protein breakdown and leading to muscle waste (Wackerhage 2014). resistance training has been showed as the most effective method to reduce the protein expression compared to endurance training (Lessard et al. 2018). This study showed that low intensity resistance training combined with blood flow restriction might enhance internal metabolic stress up to the similar extent as high intensity RT did and results in the significant reduction of Myostatin expression at post training (Laurentino et al. 2012). In Laurentino's study (2012), the low intensity resistance training group definitely trained away from fatigue and muscular failure because the repetition per set was too low, 15 repetitions; therefore, the low level of cellular stress might explain the different between two low intensity resistance training groups (Schoenfeld et al. 2013).

A year later, Martin-Hernandez et al. (2013) investigated adaptations in muscle strength and thickness after two different volumes of blood flow restriction resistance training and high intensity resistance training. 39 healthy active young students, age 20-21 years old, participated in this study. They were randomly assigned to blood flow restriction with low volume group (20%1RM 1set of 30repetitions with 3sets of 15repetitions), blood flow restriction with high volume group (doubling up volume of the first group), heavy resistance training group (85%1RM 3sets of 8repetitions). The occlusion pressure of the cuff was set at 110mmHg. Training was performed twice a week in non-consecutive days for 5 weeks. The muscle hypertrophy of rectus femoris and vastus lateralis muscles was measured via muscle thickness by ultrasonography. The results showed that the percent changes of rectus femoris muscle thickness were approximately 10%, 12%, and 10%, respectively and the percent changes of vastus lateralis muscle thickness were approximately 13%, 14%, and 12%, respectively. This was the first study that doubling the volumes of low intensity resistance training compared to high intensity resistance training. Although there was no significant different, the trend favored the doubled volume program in low intensity group might be explained by higher training volume done per session (150 repetitions vs 24 repetitions) according to the dose-response relationship (schoenfeld et al. 2017). However, it was possible that all training group already reached the maximum muscle protein synthesis ceiling. As a result, further increased workload did not obviously transfer to additional hypertrophy (Burd et al. 2012; Schoenfeld 2020).

Next, Ellefsen et al. (2015) compared the effect of 12 weeks protocols in 15 healthy untrained female participants, average age 23 years old. The within-subject research design was selected to minimize interindividual variations typically seen in training responses between human subjects. During training, one leg was assigned to perform low intensity resistance training with blood flow restriction at 30%1RM with pressurized cuff applied 90-100 mmHg during training. Training was performed 5 sets of repetition to failure with 45 seconds rest between sets. In the contrary, another leg was assigned to high intensity training which consisted of 3 sets of 6-10 repetition maximum, corresponding to 74-92%1RM, with 90 seconds rest between set. Muscle hypertrophy was assessed via MRI technique at pre and post training. The results showed that the blood flow restriction training leg significantly increased 1RM strength tested by knee extension machine (10%, $p<0.05$) while 1RM of the high intensity training leg also significantly increased up to 12% ($p<0.05$). The hypertrophic results showed that vastus lateralis muscle of both training legs significantly increased in both distal and proximal area (8% vs 6% and 7% vs 10%, respectively). In rectus femoris muscle, the cross-sectional area increased at distal area 6% and 7% in blood flow restriction and heavy training legs, respectively. However, the increased cross-sectional area at proximal area was more pronounced in high intensity leg, 9%, than blood flow restriction leg, 6% ($p<0.05$). In this study, the average muscle growth rate was 0.07% and 0.09% per day in blood flow restriction leg and high intensity legs, respectively. The physiological explanation of Burd et al. (2012) might be valid in this study that even when low intensity was used during resistance training, but if the participant kept training to muscular failure, the mechanics of fatigue would induce the recruitment of additional fibers and stimulated the same rate of muscle protein synthesis as same as high load training did. Moreover, the numbers of repetitions per session measured during week 1, 6, and 12 were substantially high (76, 103, and 106 repetitions, respectively) in low intensity RT group. This high numbers might stimulate the extent of metabolic stress which could in turn significantly affect the degree of muscle hypertrophy as well (Schoenfeld 2013)

Another study leading by Lixandrao et al. (2015) compared the training effects of different intensities and occlusion pressures in 26 healthy young adults, age between 26-29 years old. Each leg was allocated to unilateral leg extension exercise, at different intensities (either 20% or 40%1RM) and different occlusion pressure (either 40% or 80% arterial occlusion pressure). Also conventional leg was controlled either at 80%1RM without blood flow restriction. The overall picture of this study included total 52 legs: BFRT20/40 (n=11), BFRT20/80 (n=14), BFRT40/40 (n=8), BFRT40/80 (n=10), RT80 (n=9). resistance training program included 12weeks of unilateral leg extension machined, 15repetitions each set for 2-3sets twice a week. The average cuff pressures at 40% and 80% arterial occlusion pressure were around 50 and 100mmHg. The conventional heavy resistance training group did 10repetitions of 2-3sets as well. The results of training showed that quadriceps muscle cross-sectional area measured by MRI significantly increased from pre to post in all training groups (+3-5%) except BFRT20/40 (+0.78%). The between-group comparison suggested that when training at low intensity, high occlusion pressure (80%) was more significantly effective to bring hypertrophy than low occlusion pressure (40%) (+3.22% and +0.78%, respectively). However, at 40%1RM, no significant difference in low and high occlusion pressure was observed for muscle hypertrophy (40% and 80%, 4.45 and 5.30%, respectively). Conventional heavy resistance training significantly increased muscle cross-sectional area by 5.9%. In conclusion, it was possible that when very low resistance training intensity was applied, higher occlusion pressure might need to be adjusted when attempting to improve muscle mass and when training about 40%1RM, no added benefit of high occlusion pressure was noticed, therefore not be necessary (Lixandrao et al. 2015).

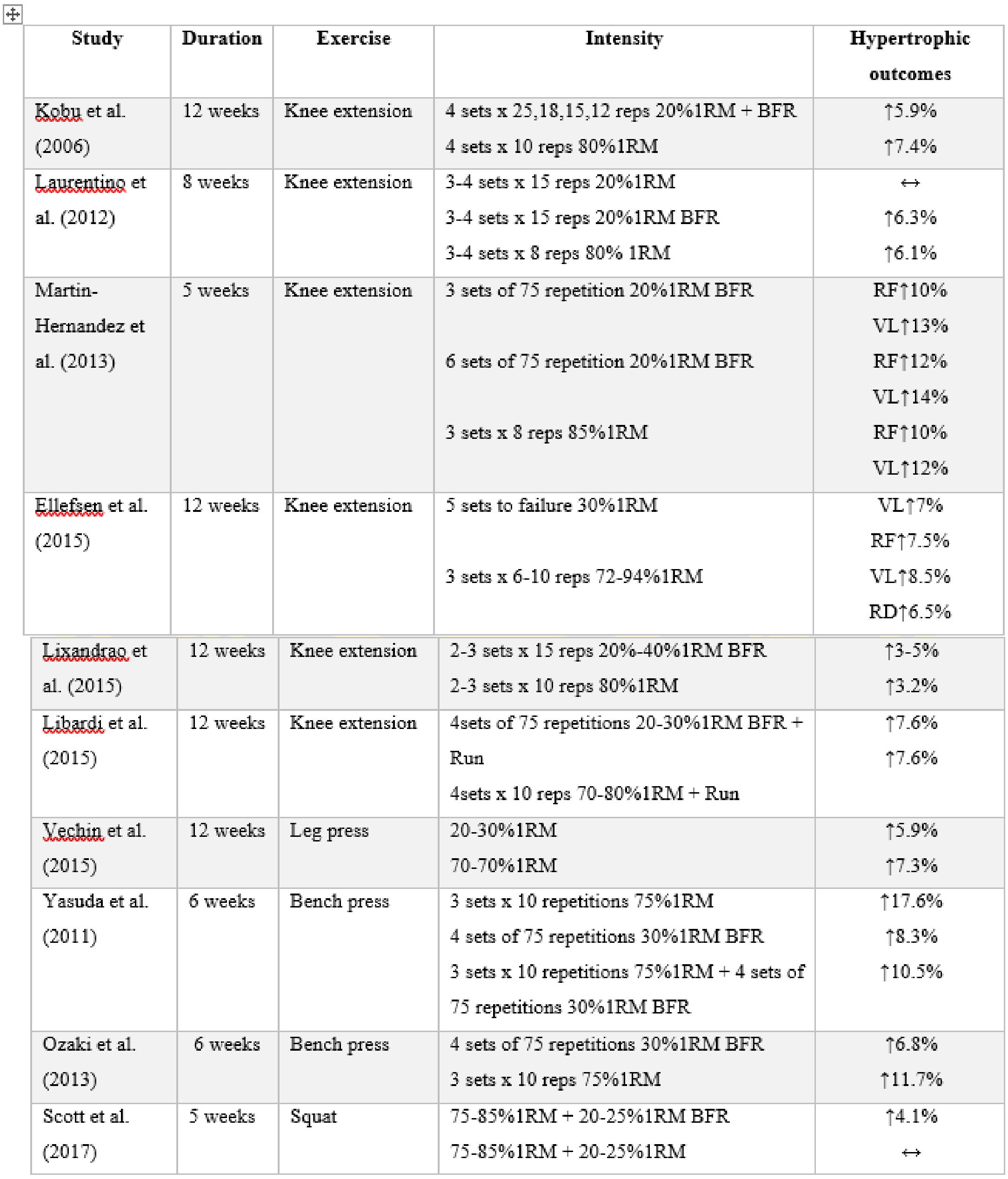
In the same year, Libardi et al. (2015) investigated the application of blood flow restriction on older participants, average age at 64 years old, who did concurrent training with blood flow restriction or concurrent training alone on the aerobic fitness test, muscle mass, and strength. 25 older sedentary but healthy participants, average age 64 years old, were randomly assigned to concurrent training: resistance training at 70-80%1RM 4x10 repetitions with 40 minute run at 60-85%VO2peak, concurrent training with moderate blood flow restriction: resistance training at 20-30%1RM 1x30 and 3x15 repetitions with cuff occlusion pressure at 50% of arterial occlusion pressure and same endurance training with the first group, and control group. The training period was 12 weeks and training frequency was 4 days a week. The results of this study suggested that the quadriceps muscle cross-sectional area significantly increased in both training groups (7.3 %, $p<0.0001$ and 7.6 %, $p<0.0001$, respectively), with no difference between group observed ($p>0.05$). In control group, there was no change in quadriceps cross-sectional area either (-2.2%, $p>0.05$). Besides, both cardiorespiratory and strength index significantly increased in both training group as well, (VO2peak +9.5%, $p=0.04$ and 10.3%, $p=0.02$, respectively; 1RM leg press + 38.1%, $p<0.001$ and 35.4%, respectively; $p=0.001$). The main different between Libardi's study and the other studies (Ellefsen et al. 2015; Laurentino et al. 2012; Kobu et al. 2006) was the aforementioned studies employed healthy young participants which were physiologically more responsible to stimuli. While it was well-documented that the numbers of structural and physiological deficits were the characteristics of aging, the response to external stimuli would probably reduce, causing difficulty to adapt (Lim & Goh 2022). The use of older participant in Libardi's study suggested that effect of blood flow restriction enhancing muscle hypertrophy when training with low intensity resistance training might be adaptable regardless of the age of participants (Libardi et al. 2015).

Vechin et al. (2015) supported the notion that blood flow restriction could be applicable to the older individuals. The researcher conducted the very well-controlled study by recruiting 23 (14 men and 9 women) older healthy adults, age between 59-71 years old, with no resistance training experience into the experiment, by randomly assigning to control, high intensity resistance training, or low intensity resistance training with blood flow restriction group. The participants performed leg press exercise 2 days per week at intensity 70-80% or 20-30%1RM, respectively for 12 weeks. In the blood flow restriction group, the cuff pressured was determined by setting at 50% of arterial occlusion pressure so the average cuff pressure was around 70 mmHg during training period. Quadriceps muscle cross-sectional area was measured pre and post training via MRI. The results suggested that both training groups significantly increased muscle cross-sectional area at post training (7.3%, $p<0.001$ and 5.9%, $p<0.001$, respectively). Despite similar increase in muscle mass, the extent by which the muscle strength increased was still significantly higher with heavy training (50%, $p<0.001$) compared to low intensity (15%, $p=0.067$). This study confirmed that effectiveness of low intensity resistance training with blood flow restriction on gains in lower limb mass in the older individuals was similar to high intensity resistance training. Nevertheless, heavy resistance training was still more beneficial when the muscle function such muscular strength was the aim of training.

When compared to most studies that usually employed lower extremity exercise, Yasuda et al. (2011) investigated the effect of upper body muscle in bench press exercise with blood flow restriction. The 40 active healthy participants, age 22-32 years old, participated in this study. The randomized controlled training groups were randomly allocated: high intensity resistance training, low intensity resistance training with blood flow restriction, combined high and low intensity resistance training, and control group. The intensity of training was 75%1RM, 30%1RM, 75% and 30%1RM respectively. High intensity group performed 3 sets of 10repetitions with 3 minute rest on bench press exercise 3 days a week while low intensity resistance training with blood flow restriction group performed 1 set of 30 repetition followed by 3 sets of 15 repetition with 30 second rest. The combined high and low intensity resistance training performed 2 days with low intensity resistance training with blood flow restriction and 1 day with High intensity resistance training. The cuff pressure was set for 100-160 mmHg during training. MRI scan was measured for pre and post training results. The finding demonstrated that the pectoralis major muscle cross-sectional area significantly increased in 3 training groups ($p<0.01$). The percent change in chest muscle cross-sectional area was highest in high intensity resistance training, followed by combined group and low intensity resistance training (+17.6%, +10.5%, and +8.3% respectively). The results of Yasuda's study suggested that although low intensity RT with blood flow restriction could enhance the hypertrophic effect of training at low intensity, the benefit of programming low intensity RT combined with heavy RT along training course might result in additional effect of hypertrophy. Not only about muscle size, the result also showed that when compared to low intensity with blood flow restriction alone, when heavy resistance training was combined, the strength gain was more pronounce in combined training group (+6.7% vs 4%). However, the greatest strength gain occurred in high intensity group (+10.5%). From many studies, we might conclude that when the aim of training for strength was prioritized, heavy resistance training was still the first-line choice if no limitation existed for that participant (Yasuda et al. 2010; Vechin et al. 2015; Ozaki et al. 2013).

Ozaki et al. (2013) further investigated the effect of blood flow restriction training on chest and triceps muscle cross-sectional area. In this study, 19 young healthy men, 22-32 years old, volunteered to participate in the randomized controlled trials. The participants were divided into high intensity RT, 75%1RM 3x10repetitions, and low intensity resistance training with blood flow restriction group, 30%1RM 1x30repetitions and 3x15repetitions. The training program included free weight bench press 3 days per week for 6 weeks. The cuff pressure was arbitrarily set at 100-160mmHg regardless of the participant's occlusion pressure. The author claimed to expect 30% reduce of brachial arterial blood flow at cuff pressure of 160mmHg as previously reported in Yasuda's (2010) study. After 6 weeks of training, the results showed that the triceps brachii and pectoral major muscles cross-sectional area significantly increased ($p>0.01$) in both heavy and low training groups (11.7% vs 6.8%, respectively).the author attributed the hypertrophic results to many mechanisms yet unclear such as accumulation of metabolites, motor unit recruitment, increased muscle protein synthesis with decreased muscle protein breakdown and possibly through an exercise-induced anabolic hormones (Ozaki et al. 2013).

There was only one study to date (Scott et al. 2017) that ever made the attempt to construct the training program that participants did the training both heavy resistance training and low intensity resistance training with blood flow restriction in one session. Scott et al. (2017) recruited 21 healthy young male Australia football players, average age 19years old to the study. All participants were familiar to resistance training that they could squat 3RM with more than 1.6 of body mass. These participants were assigned to low load group or low load with blood flow restriction group. Both groups underwent 5 weeks of well-constructed resistance training program 3 days per week, 5 different exercises (including heavy squat on Friday), 3-4 sets for each exercise at around 75-85%1RM for each set. After performing heavy resistance training, the low load group continued to perform 20-25%1RM squat for 1set of 30repetitions and 3sets of 15repetitions with 30 seconds rest between sets. The low load with blood flow restriction group also did the same protocol but adding the elastic knee wraps tightened at the proximal of both tights before beginning low load squat exercise. After 5 weeks of training, the results showed that vastus lateralis muscle thickness measured did not increase in low load group but slightly increase (+4.1%) in low load with blood flow restriction group. Therefore, from many mentioned studies, it was quite sure to infer that blood flow restriction can enhance muscle hypertrophic response when low intensity resistance training is employed.



Study	Duration	Exercise	Intensity	Hypertrophic outcomes
Kobu et al. (2006)	12 weeks	Knee extension	4 sets x 25,18,15,12 reps 20%1RM + BFR 4 sets x 10 reps 80%1RM	↑5.9% ↑7.4%
Laurentino et al. (2012)	8 weeks	Knee extension	3-4 sets x 15 reps 20%1RM 3-4 sets x 15 reps 20%1RM BFR 3-4 sets x 8 reps 80% 1RM	↔ ↑6.3% ↑6.1%
Martin-Hernandez et al. (2013)	5 weeks	Knee extension	3 sets of 75 repetition 20%1RM BFR 6 sets of 75 repetition 20%1RM BFR 3 sets x 8 reps 85%1RM	RF↑10% VL↑13% RF↑12% VL↑14% RF↑10% VL↑12%
Ellefsen et al. (2015)	12 weeks	Knee extension	5 sets to failure 30%1RM 3 sets x 6-10 reps 72-94%1RM	VL↑7% RF↑7.5% VL↑8.5% RD↑6.5%
Lixandrao et al. (2015)	12 weeks	Knee extension	2-3 sets x 15 reps 20%-40%1RM BFR 2-3 sets x 10 reps 80%1RM	↑3-5% ↑3.2%
Libardi et al. (2015)	12 weeks	Knee extension	4sets of 75 repetitions 20-30%1RM BFR + Run 4sets x 10 reps 70-80%1RM + Run	↑7.6% ↑7.6%
Vechin et al. (2015)	12 weeks	Leg press	20-30%1RM 70-70%1RM	↑5.9% ↑7.3%
Yasuda et al. (2011)	6 weeks	Bench press	3 sets x 10 repetitions 75%1RM 4 sets of 75 repetitions 30%1RM BFR 3 sets x 10 repetitions 75%1RM + 4 sets of 75 repetitions 30%1RM BFR	↑17.6% ↑8.3% ↑10.5%
Ozaki et al. (2013)	6 weeks	Bench press	4 sets of 75 repetitions 30%1RM BFR 3 sets x 10 reps 75%1RM	↑6.8% ↑11.7%
Scott et al. (2017)	5 weeks	Squat	75-85%1RM + 20-25%1RM BFR 75-85%1RM + 20-25%1RM	↑4.1% ↔

Table 4. Previous studies compared hypertrophic outcomes between high- and low-intensity RT BFR

4.2 Duration of training intervention for muscle hypertrophy

The duration of training for muscle hypertrophy varied based on several factors such as individual goals, current fitness level, and training experience. Generally, a typical training program for hypertrophy in literature lasts anywhere from 4 weeks to 12 weeks, with progressively increasing volume over time. However, some advanced trainees may need longer programs to continue making progress, while beginners may see results in a shorter timeframe such as 6 weeks. Additionally, it's crucial to regularly assess progress and adjust the training program as needed to ensure continued muscle growth. Ultimately, consistent and progressive training is the key to achieving muscle growth.

In the meta-analysis of Krzysztofik et al. (2019), the researchers included 9 high quality studies which the randomized controlled trial design was implemented and using BFR technique for the purpose of muscle hypertrophy training. The length of RT duration varied from 4 weeks (Lowary et al. 2014; Yamanaka et al. 2012), 6 weeks (Farup et al. 2015; Cook et al. 2018; Yasuda et al. 2011), 8 weeks (Laurentino et al. 2012), and 12 weeks (Kubo et al. 2006; Ellefsen et al. 2015; Lixandrao et al. 2015). All these studies reported the significant increase in muscle hypertrophy after training.

The protocol of BFR in these studies ranged around 20-40%1RM. The effectiveness of using BFR concerns various populations such as non-athletes (Laurentino et al. 2012, Lixandrao et al. 2015), moderately experienced participants (>1 year) (Lowery et al. 2014), and elite athletes (Yamanaka et al. 2012; Cook et al. 2018).

When considering the duration of low intensity RT with BFR and its effect on muscle hypertrophy, short duration seems to be sufficient to get this purpose done. In the study conducted by Farup et al. (2015), the results showed that after 6 weeks of RT, a statistically significant increase in the muscle cross-sectional area of the biceps brachii, as measured by magnetic resonance imaging, was observed in 10 young men, with a tangible increase of 11.5%. The intensity employed in this study was 40% of 1RM with the use of the BFR technique and repetitions were performed until failure in every set. The findings of Yasuda et al. (2011) were consistent with this study, as they employed an intensity of 30%1RM with the BFR technique using the bench press exercise in 13 young men. After 6 weeks of RT, they observed hypertrophies of the triceps brachii and pectorialis major muscles, with increases of 8.8% and 15.8%, respectively. Another study by Ozaki et al. (2013) also investigated the effect of low intensity with blood flow restriction at 30%1RM in bench press exercise as well. They found in 19 healthy men that the muscle cross sectional areas of triceps brachii and pectorialis major muscles, data in combined, increased significantly up to 6.8% from pre training. This observation was also supported by Cook et al. (2018) in lower limb muscles, who found that after 6 weeks of leg press and knee extension exercises, 18 healthy men showed a significant increase in quadriceps muscle hypertrophy, with a 2.5% change from pre-training measurements. It appears that low intensity resistance training with blood flow restriction is equally effective in inducing substantial muscle hypertrophy in both upper limb and lower limb muscles, as demonstrated by the results of multiple studies (Farup et al. 2015; Cook et al. 2018; Yasuda et al. 2011). A duration of 6 weeks has been found to be sufficient for eliciting observable increases in muscle size, regardless of the specific muscle group being targeted.

The findings from these studies indicate that blood flow restriction training of a duration of 6 weeks appears to be adequate for eliciting observable muscle hypertrophy, as evidenced by statistically significant differences when compared to pre-training measurements. This conclusion is in line with the findings of Damas (2018), who posited that muscle hypertrophy is a complex process requiring a specific period of time for development to occur. During the early weeks of training, muscle growth may appear to be due to muscle damage-induced swelling and inflammation, however, these conditions are temporary and can be misleading as indicators of true muscle hypertrophy. According to Damas et al. (2018), muscle damage tends to be most pronounced during the first 3 weeks of training. As such, measuring muscle hypertrophy during this period may be inappropriate. In order for true muscle hypertrophy to be observed, it is recommended that a minimum of 6 weeks of consistent resistance training be completed to allow for the mitigation of muscle damage (Damas et al. 2018).

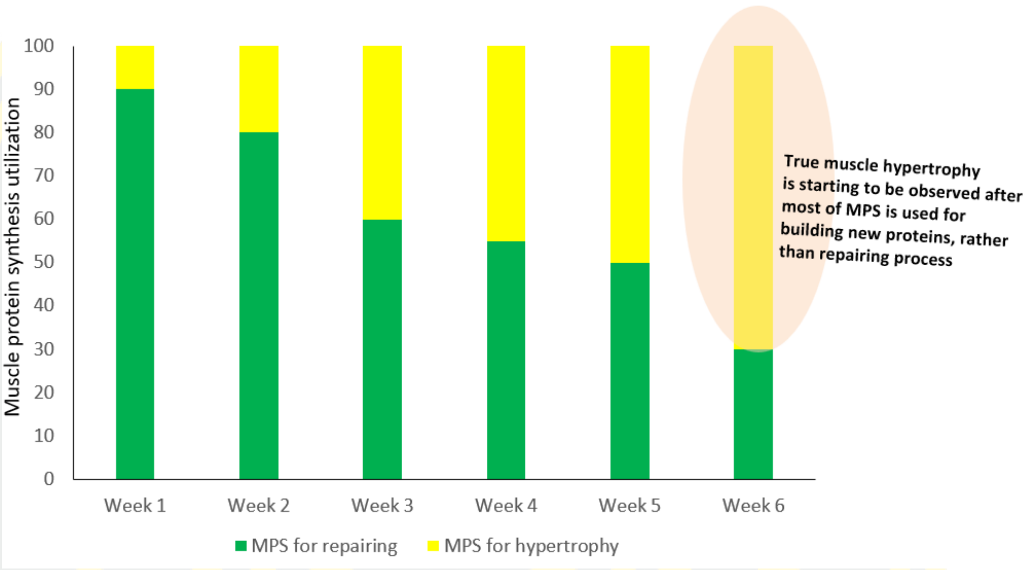


Figure 24. Duration for true muscle hypertrophy to be observed.

5. Application of blood flow restriction

In order to implement blood flow restriction technique, the most important issue to consider is the pressure of the cuff applied on trainee's limbs. There are numerous approaches to determine how much pressure the researcher is going to utilize. Some methodologies are referred as ***clinical blood flow restriction or (cBFR)*** such as the non-individualized arbitrary pressure technique (e.g. Evans et al. 2010), percentage of limb occlusion pressure technique (e.g. Sousa et al. 2017), and brachial systolic blood pressure technique (e.g. Takada et al. 2012) while some methodologies are referred as ***practical blood flow restriction (pBFR)*** because the researcher can not measure the exact numeric pressure but they adjust the tightness based on other references such as perceived tightness technique (e.g. Luebbers et al. 2019), absolute and relative overlap technique (e.g. Yamanaka et al. 2012) and maximal cuff elasticity technique (e.g. Behringer et al. 2017).

5.1 Clinical blood flow restriction

In research settings, both ***cBFR*** and ***pBFR*** offer unique advantages. With cBFR, researchers can precisely control the cuff pressure applied to the muscle. However, determining the "optimal pressure" is more complex than it appears (Torpel et al. 2018). For instance, while a researcher may set the cuff pressure at 100mmHg, the effect of this pressure can vary significantly between individuals due to several factors, including systolic blood pressure, body fat, body composition, and even cuff placement (Bielitzki et al. 2021). ***Despite the lack of a universally accepted methodology for applying blood flow restriction, there is a consensus among researchers that pressure should be individualized based on arterial occlusion pressure (AOP)*** (e.g., Fahs et al. 2014; Lixandrao et al. 2015; Gaviglio et al. 2015). AOP, or limb occlusion pressure (LOP), involves inflating the cuff until blood flow to the muscle is fully occluded, identifying this point as 100%AOP/LOP, and then setting the cuff pressure as a percentage of this full occlusion (Petterson et al. 2019).

The literature reveals that occlusion pressures range widely, from as low as 40% AOP (e.g., Hill et al. 2018) ***to 50%*** (e.g., Santos et al. 2014), ***60%*** (e.g., Mendonca et al. 2021), ***70%*** (e.g., Mattar et al. 2014), ***80%*** (e.g., Laurentino et al. 2012), ***and even up to 100%*** (Laurentino et al. 2008). Laurentino et al. (2008) conducted the only study to date that used 100% AOP, involving 16 healthy, physically active men. The study compared the effects of resistance training at 6RM versus 12RM. The right leg of each participant was trained using cBFR at 100%AOP, while the left leg served as a control. Participants performed 3-5 sets per week with a 120-second rest period. After 8 weeks, no adverse effects were reported, except for a high degree of discomfort in the high intensity group.

This study was atypical for cBFR research, as most studies use intensities around 20-50%1RM (Wernbom & Aagaard 2020). Thus, it is not surprising that lifting a heavy load (6RM or approximately 85% 1RM) with very tight restriction (100% AOP) caused noticeable discomfort. Nonetheless, the study demonstrated that even high intensity resistance training with 100%AOP is still safe for healthy, trained individuals (Laurentino et al. 2008).

The recent position stand on blood flow restriction recommends practitioners use a 75-repetition scheme (30x15x15x15) or train to failure with 40-80% AOP. Occlusion pressures within this range are considered sufficient to induce adaptations and provide a safe training stimulus, while pressures above 80%AOP, though safe, may not be necessary (Patterson et al. 2019).

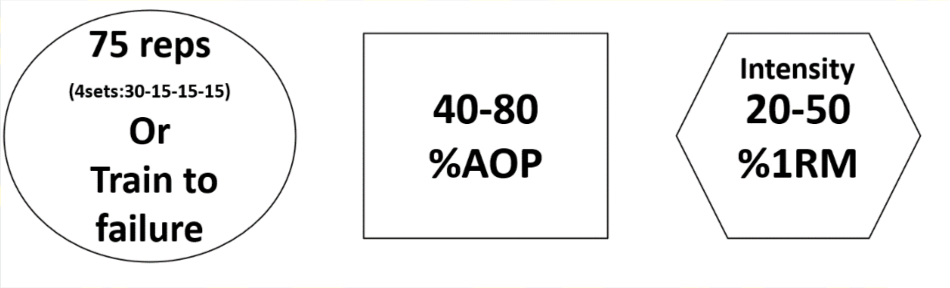


Figure 25. The position stand on blood flow restriction protocol for hypertrophy.

In hypertrophy-focused research area, studies showed that low %AOP (e.g. 40%AOP) was efficacious to induced increase in muscle mass after period of training. For example, Lixandrao et al. (2015), as earlier mentioned, found that both at 40%1RM of unilateral knee extension exercise, both AOP of 40% (mean pressure about 55mmHg) and 80% (mean pressure about 105mmHg) produced the similar results in muscle hypertrophy after 12 weeks of training (4.45% vs 5.30%, respectively). In the same way, Jessee et al. (2018) assigned 46 healthy resistance-training naive participants to train knee extension exercise at 15%1RM with cuff pressures of 40%AOP on one leg and the other leg with cuff pressure of 80%AOP. They trained twice a week of 4 sets of repetition to failure for each session. After training, muscle thickness at anterior and lateral sites of quadriceps muscle was measured via ultrasound technique. The results showed that at anterior site, there were the significant increases in muscle thickness at 30% (+0.05cm vs +0.17cm), 40% (+0.14cm vs +0.19cm), 50% (+0.18cm vs +0.17cm), and 60%(+0.21cm vs +0.20cm) of femur length in both 40%AOP and 80%AOP conditions, respectively. At lateral site, the significant increases in muscle thickness were also evident in conditions at all sites measured (+0.02cm vs +0.17cm, 0.13cm vs +0.09cm, 0.12cm vs +0.07cm, 0.18cm vs +0.10cm) in 40%AOP and 80%AOP conditions respectively.

It was convincible from the existing evidence that the selection of occlusion pressure was varied for choice of preference. However, only low occlusion pressure might suffice to elicit hypertrophic response. Mechanistically, the recent study by Mouser et al. (2017) found although the cuff pressure was increased linearly, the change of hemodynamics of muscle blood flow might not be significantly different, not linear. They found that from 50%AOP up to 90%AOP, the muscle blood flow reduced in non-linear fashion that there was no difference between the pressures. In this study, total 43 participants reported average muscle blood flow at rest at 50.3 ml/min. When the blood flow restriction was applied at 10%AOP, 20%AOP, 30%AOP, and 40%AOP, they found that muscle blood flow significantly reduced in linear fashion (42.0, 33.6, 23.6, and 17.1 ml/min, respectively). However, when the cuff pressured was adjusted to 50%-90%AOP, the hemodynamic flow did not significantly change among pressures (12.5, 11.5, 11.4, 10.3, and 7.9 ml/min, respectively). ***Therefore, it could be not necessary, although possible, to impose higher pressure over 50%AOP because over this point muscle blood flow remained almost unchanged***.

Moreover, it is well-documented that applying ***a higher percentage of arterial occlusion pressure is associated with greater perceptual responses, such as increased discomfort and a higher rate of perceived exertion*** (Mattocks et al. 2017). These factors may contribute to a reduction in total training volume and time under tension, both of which are critical for muscle hypertrophy (Schoenfeld et al. 2017). However, an advantage of recognizing the pressure applied during cBFR is that it can be adjusted, potentially lowering the risk of injury, particularly in individuals requiring special care, such as the elderly or patients with musculoskeletal conditions. Despite this, the high cost and complexity of using clinically reliable equipment make cBFR less accessible for many researchers and impractical for real-world training settings (Loenneke et al. 2011).

Another approach to determine the occlusion pressure is to use non-individualized pressure that the research has predetermined the exact numeric pressure that will be used regardless of the individual's occlusion pressure. The systematic review of Murray et al. (2021) covered 129 studies that used blood flow restriction technique during exercise both RT and aerobic training and reported that more than 56% of total included studies employed this non-individualized pressure approach or sometimes known as ***arbitrary pressure approach***.

The range of arbitrary pressures used during resistance training varies widely depending on the researcher, with pressures ranging from as low as ***50 mmHg*** (Sugiarto et al. 2017) to as high as ***250 mmHg*** (Madarame et al. 2011). Examples include ***100 mmHg*** (Nielsen et al. 2012), ***130 mmHg*** (Taylor et al. 2016), ***218 mmHg*** (Takarada et al. 2004), and ***230 mmHg*** (Kacin & Strazar 2011). However, the use of arbitrary pressures, although common in the literature, can be problematic. It often overlooks individual differences, such as limb size, which may not only reduce the effectiveness of the training but also raise safety concerns (Loenneke et al. 2013).

In hypertrophy-focused research area, studies also proved the effectiveness in application of arbitrary pressure as well. For example, Sugiarto et al. (2017) compared the increase in muscle hypertrophy in high- (70%1RM) and low-intensity resistance training (30%1RM) with blood flow restriction at 50 mmHg pressure. Biceps curl was the main exercise performed in this study. All 18 healthy participants trained twice a week for 5 weeks. The results showed that the muscle circumference after 5 weeks of strength training significantly increased in high intensity and low intensity with blood flow restriction group (+1.58cm and +1.48, both *p<.0001*, respectively). At little higher pressure at 110mmHg, the aforementioned study of Martin-Hernandez et al. (2013) also did prove its effectiveness in eliciting muscle hypertrophy as well. The researchers found that low intensity combined with blood flow restriction cuff set at 110mmHg significantly elicit muscle hypertrophy to the similar extent and high intensity RT after 5 weeks of training (+7.03%, p<0.05 and +6.24%, p<0.05, respectively).

In many studies, ***the arbitrary occlusion pressure of blood flow restriction might be progressively increased in every week of training*** (e.g. Yasuda et al. 2010; Yasuda et al. 2011; Yasuda et al. 2012). For example, a study investigated the hypertrophic effect of blood flow restriction training on multi-joint exercise bench press in 10 young healthy men, age 23-28 years old (Yasuda et al. 2010). During training program, participants were randomly assigned to low intensity 30%1RM blood flow restriction training group or low intensity group with free blood flow. The training program included free weight bench press, 4 sets of total 75 repetitions, twice daily, for 6 days per week for 2 weeks. The progression of pressure was increase 10mmHg, starting from 100mmHg, until 160mmHg was reached. The results demonstrated that even though the duration of training was quite short, the muscle thickness of triceps brachii and pectoralis major was significantly increased by 8% and 16% (both p<0.05) in only low intensity with blood flow restriction group. However, no significant changes were observed in free blood flow group in both triceps brachii and pectoralis major muscle.

Another study that used progressive pressure by Yasuda et al. (2011) investigated the training effect on limb and trunk muscle hypertrophy in 30 young men, age 23-25 years old, dividing into high intensity 75%1RM group, low intensity 30%1RM with blood flow restriction group and control group. The bench press exercise was performed

3 days per week for 6 weeks in a row. Blood flow restriction pressure was also set at starting 100mmHg and then increased by 10 mmHg each day until a final training pressure of 160 mmHg was reached. High intensity group performed 3 sets of 10 repetitions while the blood flow restriction group performed 1 set of 30 repetitions following by 3 sets of 15 repetitions. The results showed that after training, the significant increase in muscle hypertrophy of triceps brachii (+8.6% and +4.9%) and pectoralis major (+17.6% and +8.3%) muscles was observed in both high and low intensity group, respectively. Although the size gain was similar, 1RM via bench press test significantly increased to higher extent ($p<0.01$) in high intensity group (+19.9%) than low intensity group (+8.7%), respectively.

At the very high pressure over 200mmHg, study also proved its effectiveness on muscle hypertrophy. Madarame et al. (2008) investigated given that if blood blow restriction training had been showed to induce strong hormonal response, whether or not its effect of hypertrophy would be transferred to non-training arm. 15 healthy untrained men, average age 21 years old, were recruited into study and randomly assigned to group occlusive training and group normal training. Both groups had one arm training with unilateral dumbbell curl for 3sets of 10repetitions at 50%1RM with 180second rest interval. The restriction pressure was set starting at 160mmHg and increased 20mmHg every 2 weeks until reaching 240mmHg in week 10. After 10weeks of training, the results demonstrated that muscle cross-sectional area measured via MRI showed that the cross-sectional area of biceps brachii muscle increased significantly only in occlusive training arm (approximately 5%, $p<0.05$) when compared to baseline (from 34.8cm^2 to 36.8cm^2). No significant change was observed in normal training arm (from 32.4cm^2 to 32.5cm^2). Besides, the transfer effect was not occurred either from arm training with blood flow restriction or normal training, indicating that the role of hormonal response for hypertrophy might be invalid.

In older adults at the very high pressure over 250mmHg, arbitration blood flow restriction pressure also proved it safety and effectiveness in eliciting muscle hypertrophy as well. A study in 17 older adults including both men and women, age between 61-85 years old demonstrated that even in the elderly progressive increase of blood flow restriction pressured was so safe and effectively inducing muscle hypertrophy after 12 weeks of training. Yasuda et al. (2015) divided participants into 2 groups: with and without blood flow restriction, and then employed resistance training by the use of elastic bands. None of the older adults in this study had participated in resistance-type training before entering the study. The researcher assigned "heavy green band" for men and "thin yellow band" for women. Training programs included arm curls and triceps pushdown exercises with volume of 75 repetitions (30, 15, 15, and 15 repetitions, with 30-second rests between sets) for each exercise with 90second rests between exercises. Blood flow restriction pressure was starting at 120mmHg and progressively increased in each subsequent training session by 10-20mmHg until ending at 270mmHg. The amount of time under BFR was approximately 11 minutes. The results showed that biceps brachii and triceps brachii muscles cross-sectional areas significantly increased in the group of the older adults who trained with blood flow restriction only (+17.6%, p<0.0001 and +17.4%, p<0.0131, respectively). However, no significant change was observed in free blood flow group.

Another method to set the cuff restriction pressure is to apply to relative pressure based on participant's systolic pressure (SBP) (Loenneke et al. 2013). However, there was no consensus in applications that in many studies, ***some researchers applied the blood flow restriction cuff pressure higher than SBP*** (e.g. Item et al. 2011; Clark et al. 2011; Mueller et al. 2014) while ***some contrarily applied lower cuff pressure than this reference SBP*** (e.g. Bond et al. 2017; Ramis et al. 2018). Moreover, the cuff size became problematic when using this method. If the cuff used for blood pressure measurement was not as the same size as the cuff used during exercise, the reduction of blood flow might not be consistent. For example, Loenneke et al. (2013) demonstrated that with a wide 13.5cm cuff, the application of blood flow restriction at 130% of brachial SBP resulted in arterial occlusion in 49 out of 116 participants. In contrast, if the cuff width was 5 cm, only 1 out of 83 participants would experience arterial occlusion at pressure of 130% brachial sBP. Furthermore, Loenneke et al. (2013) claimed that most of the time SBP was measured via brachial artery at arm and although its application in upper limb would be reliable, it might not be a good estimate of arterial occlusion in the lower limb because the nature of larger circumference of thigh would require higher restriction pressure to induce arterial occlusion (Loenneke et al. 2016). Therefore, the reliability would be questionable when application of blood flow restriction cuff in lower limb with relative cuff pressure based on brachial SBP.

In hypertrophy-focused research area, studies also proved the effectiveness of application blood flow restriction cuff pressure based on brachial SBP. For example, it was demonstrated that the muscle preservation effect, although not direct hypertrophy, could be induced by low intensity blood flow restriction resistance training during muscle disuse period Cook et al. (2010) applied the blood flow restriction with 6 cm cuff width and pressure at 130% of participant's resting brachial SBP. Participants were 16 young healthy adults, age 18-26years old, randomly assigned into two groups. The unilateral lower limb suspension (ULLS) group and ULLS with resistance exercise with blood flow restriction group. Both groups underwent 30days of lower limb suspension. The exercising group still performed 3 sets of dynamic knee extension exercise at 20% of maximal voluntary contraction for 3 days per week while the other group did nothing. After 30 days of limb suspension, the group that underwent RT, albeit low intensity, with blood flow restriction experience only minimal loss of strength and muscle mass (2.0% and 1.2%, respectively), while the group that performed no exercise demonstrated the significant reduction in both strength and mass (21% and 7.4%, respectively).

Another study by Gorgery et al. (2016) examined the effect of neuromuscular electrical stimulation on muscle cross-sectional area in 9 spinal cord injury patients. The program included 6 weeks of electrical stimulation with blood flow restriction in right wrist extensor muscles while the left wrist extensor received electrical stimulation only without blood flow restriction. The blood flow restriction pressure was set at 30% above resting brachial SBP. After 6 weeks of training, the cross-sectional area of extensor carpi radialis longus muscle increased by 17% (absolute change of 0.6 cm^2; $p=0.048$) in only group applied blood flow restriction. However, no significant pre to post intervention change in muscle cross-sectional area in group with electrical stimulation only was observed.

Moreover, when applied blood flow restriction, it was possible to deflate the pressure down during the rest interval when the applied pressure was so high. For example, study that employed SBP as a reference point was conducted by Item et al. (2011). The researchers recruited 21 young healthy women, average age 23 years old, to the study and randomly assigned to training and control group. The participants in training group performed a resistance exercise for 3 days per week for 5 weeks. The exercises included squat and heel rise for 3 sets each with a task cycle of 4 minutes on and 1 minute off. Blood flow restriction pressure was set above SBP, referred as ***supra-systolic pressure***. The supra-systolic pressure was the highest pressure that each participant could tolerate for the duration of task cycle. The average supra-systolic pressure was 197mmHg used in this study. During the rest 1 minute off, the pressurized cuff was deflated to a pressure 100mmHg. The loads for squat and heel rise were set at 57% and 61% of body mass and gradually decreased in the second and third set. The result showed that training group significantly increased fiber cross-sectional area of type l and type ll fiber for 16.7 % and 13.8 %, respectively. Accordingly, the lean thigh mass measured via dual-energy x-ray absorptiometry showed the significant increase by 4% in training group (10.6kg to 11kg ($p=0.001$).

Another study that used supra-systolic pressure was conducted by Mueller et al. (2014). 26 endurance-trained men participated in this study and were randomly divided to training with vibration group and normal resistance training group. The training program for both groups included squat at 70%1RM for first set and the load was gradually reduced by approximately 10 % for each of the following sets to induce volitional muscle failure within 60-100 s of exercise. The training with vibration group also added the blood flow restriction cuff at that highest pressure tolerable by the participants and low frequency vibration when training. The cuff pressure was maximal at 200mmHg during training and deflated to 100mmHg during rest. The finding demonstrated that thigh lean mass significantly increased by 3.1% ($p<0.01$) in the training with vibration group, whereas only slight increase was observed in the normal resistance training group (+1.2 %, $p=0.074$), significantly different between group ($p<0.01$).

From existing literature and those mentioned earlier above in this part, it was showed that ***all approaches of applications of cBFR proved its effectiveness and safety in inducing muscle hypertrophy***. However, the matter of nuance lies in the cost, accuracy in manipulation, and expertise of the researchers. It seemed that there were choices of preference in different group of researchers to select the clinical approach in their favors. However, one problem about cBFR is its practicality in real training setting. Due to the difficulty to adjust pressure and cost of affordability of clinical device capable of regulating the restriction pressure, pBFR was for the first time introduced by Loenneke et al. (2009) to substitute cBFR in practical setting.

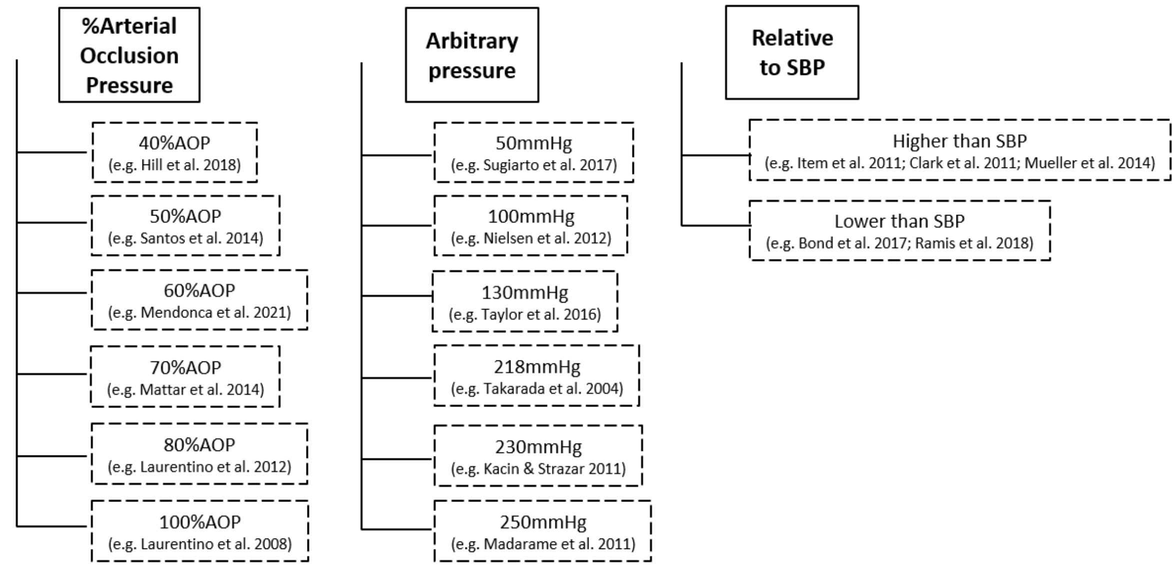


Figure 26. Methodology for applying blood flow restriction.

5.2 Practical blood flow restriction

In simple term, ***practical blood flow restriction (pBFR) is the use of elastic band such as knee wrap, instead of clinical pressurized cuff to restrict arterial inflow and occlude venous outflow***. Due to its inexpensiveness and accessibility, it provides the feasible option for the general population exercising at their local gym for blood flow restriction training (Loenneke et al. 2009; Mattocks et al. 2018; Rolnick et al. 2020). ***However, the reason that the pBFR can not be accurate about how much pressure is being applied makes this disadvantage its big stigma in research setting***. However, many researchers had made and attempt to standardize the way to apply pBFR during the past years (e.g. Wilson et al. 2013; Abe et al. 2019; Freitas et al. 2021).

One of the most common approaches of application of pBFR in literature was using perceived pressure technique (Lowery et al. 2014; Head et al. 2015; Scott et al. 2017). This technique was initially proposed by Wilson et al. (2013). Back then the researchers investigated the effects of moderate pBFR on metabolic stress, muscle swelling, and skeletal muscle activation as well as to validate a practical method to cBFR. 12 college healthy men were recruited into the study, average age 21 years old.

They were introduced to pBFR with elastic wraps of 7.6cm wide. The researchers also introduced the perceived pressure scale to participants, explaining that 0 out of 10 was no pressure at all applied, that 10 out of 10 was where the intense pain occurred, and that 7 out of 10 was moderate pressure but still no pain. The knee wraps were tightened proximally on the femur and allowed for several wraps around until perceived pressure scale of 7 was reached. Afterwards, the researcher used ultrasound probe to detect the femoral artery at popliteal region to validate the method. The results showed that at the reported pressure of 7 out of 10, the femoral vein was completely restricted but not artery in all participants. When the reported pressure reached 10 out of 10, 8 participants had their artery completely restricted. As a result, it was suggested that the perceived pressure of 7 out of 10 was consistently resulting in complete venous constriction; therefore, it could be served as a valid alternative to the cBFR (Wilson et al. 2013). Moreover, in this study, they also confirmed that pBFR based on perceived pressure technique could induce metabolic stress and muscle swelling as same as cBFR as showed that after 4 sets (1set of 30 and 3 set of 15repetitions) of 30%1RM leg press, muscle thickness at immediately, 1- and 5-minute post exercise significantly increased ($p<0.0001$) and blood lactate after training was also higher in pBFR (6.2 vs 4.7mmol/L). Moreover, muscle activation was also significantly higher during low intensity blood flow restriction in the last set compared to non-restriction group ($p<0.05$) (Wilson et al. 2013).

In hypertrophy-focus research area, numbers of studies that utilized perceived pressure technique also proved its effectiveness to induce the satisfying results. For example, Lowery et al. (2013) examined the effects of pBFR on hypertrophy of arms. In this study, 20 healthy college men volunteered, average age 23 years old with a minimum 1 years of RT experience. The crossover design was employed that participants either training with pBFR in the first 4 weeks followed by 4weeks of high intensity training (BFR-HI) or training high intensity first and with pBFR in the last 4 weeks (HI-BFR). Total 8 weeks of training program, twice a week, was constructed. The exercise that would utilize pBFR was biceps curl. For the pBFR biceps curl exercise, the elastic knee wraps of 7.6cm wide was applied at the proximal portion of the upper arm at the perceived pressure of 6-7 out of 10, following the valid recommendation of Wilson et al. (2013). For the non-pBFR bicep curl exercise, participants were also wrapped with elastic knee wraps but with tension of 0 out of 10 to control any confounds. The intensity of exercise was 4 set of 75 repetitions scheme (30-15-15-15) at 30%1RM during low intensity training. In order to control the training volume between conditions, the non-pBFR condition performed 15 repetitions at 60%1RM instead for the first set. The results, no matter the order of program, showed that the muscle thickness of biceps brachii muscle via ultrasound measurement significantly increased in both BFR-HI and HI-BFR conditions from baseline to week 4 (6.9% and 8.6%, $p<0.01$) and from week 4 to week 8 (4.1% and 4.0%, $p<0.01$), indicating both combinations of a periodized RT program were effective. When the training volume was matched, the order of intensity might depend on the choice of preference.

Years later, Head et al. (2015) also employed inexpensive elastic wraps for pBFR to examine the training effects on muscle strength, functions, and hypertrophy. The perceived pressure technique was utilized during application of 7 out of 10 wrapping pressure according to Wilson et al. (2013). The elastic knee wraps of 7.6 wide was applied at the proximal portion of thighs. In this study 12 healthy participants were recruited into the experiment dividing into pBFR and control group. The single leg squat program, twice a week for 6 weeks was instructed for both groups. During the first 3 weeks, participants performed squat at the depth of 75 degree of knee flexion for 3-4 sets and the last 3 weeks, the depth of squat was progressively increased to 90 degree of knee flexion for 4 sets, with 1-minute rest in every week. All set was performed to point of fatigue. The results showed that thigh circumference slightly, but not significantly, increased in both pBFR and control group (49.4 to 49.7cm and 50.4 to 51cm). In part of muscle strength, it was showed that muscle concentric peak force increased significantly only in pBFR group (83.2 to 91Nm, $p<0.05$) while no significant change was observed in control group. In other variables of performance, such as eccentric peak force, isometric peak force, and vertical jump, there was no significant change observed in both training group from pre to post testing. Although, no statistically significant increase in thigh circumference was observed in this study, it showed that pBFR might facilitate strength gain compared to normal training.

Another study utilizing Wilson's (2013) perceived pressure technique with pBFR in training – also the key paper providing the knowledge gap for this dissertation – was conducted by Scott et al. (2017). As aforementioned in previous section, Scott et al. (2017) employed pBFR in supplementation to normal high intensity resistance training. The elastic knee wraps 7.5cm wide, 250cm long were initially applied at the proximal thighs without tension during high intensity resistance training and just before the start of supplementary workout the researchers tightened the wraps until participants reported pressure of 7 out of 10. However, as mentioned earlier, the experiment of this study did not elicit significant change in muscle hypertrophy variable maybe due to some confounding factors such that the set was not taken to failure and participants were used to years of resistance training and duration of training was too short for semiprofessional lifter to obtain the training effect.

Apart from the popular perceive pressure technique that was often employed to standardize application of pBFR in research setting, there were some more techniques existing in the literature that successfully elicited hypertrophic outcome. For example, the overlap technique (Yamanaka et al. 2012; Bjornsen et al. 2019; Luebbers et al. 2019) is simply explained that the researchers pull the elastic wrap around the target limb and end with the overlap manner in the particularly needed length, such as 2-5 inches overlap.

The first study that employed the overlap technique was conducted by Yamanaka et al. (2012). The researchers investigate the effect of 4 weeks low intensity resistance training with pBFR on upper and lower body muscular hypertrophy and strength in football athletes. 32 college football athletes, average age 19 years old with 5 years in RT experience, were recruited into the study and divided into intervention group and control group. The training program included 4 sets of squat and bench press, 3 times per week for 4 weeks. The intervention group performed low intensity resistance training at 20%1RM with pBFR, 1 set of 30 repetitions followed by 3 sets of 20 repetitions, with 45 second rest between sets. The control group also performed the same resistance training program but with not pBFR applied. Blood flow restriction was applied in the same manner in all participants, by using elastic wraps of 5cm wide tightening at the proximal of arms and thighs to restrict brachial artery and femoral artery, pulling to overlapped end by 2 inches and firmly secured. The elastic bands were immediately released after exercise. After 4 weeks of training, the results showed that the muscle hypertrophy was observed in every point measured in both group but to the higher extent in pBFR group. For example, upper chest girth increased by 3.8cm and 1cm; lower chest girth increased by 2.5cm and 1.2cm; right thigh increased by 1.2cm and 0.7cm; leg thigh increased by 1.1cm and 0.5cm, in pBFR group and no pBFR group, respectively. Moreover, when it came to muscular strength, 1RM squat and bench press were also significantly increased to higher extent in pBFR group than no pBFR group (+8% and 7% vs +4.9 and 3.2%, respectively). This was the first study in literature that introduced the use of overlap technique and successfully induced increased hypertrophy, albeit not measured with gold standard technique, and strength. However, the problem of this technique was that with the nature of elastic wraps, it tended to be loose and more stretching everything it was used; therefore, the internal validity of equipment might decrease over time.

Another study that employed the overlap technique was Bjornsen et al. (2019). The researchers had found that type 1 fiber significantly hypertrophied after short training block of pBFR was introduced in earlier sessions. The researchers recruited 16 men and 3 women elite powerlifters, average age 25 years old, to the study. They were never training under any blood flow restriction protocol prior to this study. All participants were assigned to blood flow restriction group and conventional group. The training program lasted for total 6 and half weeks but during the week1 and 3, the blood flow restriction group performed 5 session of low intensity front squat with pBFR. The intensity was around 24-31%1RM in low intensity session. In contrast, the conventional group continued to perform normal front squat 60-85%1RM, 6-7sets of 1-6 repetitions per set. For the rest of 6 and half week program, both groups performed the same training protocol including variations of squat, deadlift, bench press, biceps and triceps exercise at 60-85%1RM for 6-7 sets. The pBFR was done by using elastic knee wraps of 7.6cm wide tightening around the proximal part of the thigh and pulling to the overlapped end by 5-5.5 inches before starting the set. This protocol of pBFR should result in the pressure approximately 120mmHg as claimed by the authors. After training ended, the muscle cross-sectional areas of quadriceps muscles were measured via ultrasound technique, as well as muscle biopsy samplings were performed. The results showed that the cross-sectional area of vastus lateralis muscle significantly increased in blood flow restriction group (+1.64cm^2) compared to conventional group (+0.12cm^2). Moreover, the cross-sectional area of rectus femoris muscle also significant increased more in the blood flow restriction group (+0.97cm^2) compared to conventional group (0.21cm^2). Besides, muscle biopsy results demonstrated that type l fiber cross-sectional area significantly increased only in blood flow restriction group (+974 vs +13μm^2). The interesting find of this study was the preferential type l hypertrophy in blood flow restriction group which was quite contrary to normal heavy RT that usually resulted in type ll fiber hypertrophy. The author hypothesized that blood flow restriction training might put more stress on type l fiber during training to failure with low intensity. Therefore, it was probably that low intensity blood flow restriction training might serve as a novel stimulus for the type I fibers hypertrophy in elite powerlifters and these fibers probably had a large potential to hypertrophy (Bjornsen et al. 2019).

Apart from muscle hypertrophy, Luebbers et al. (2019) investigated the effect of pBFR resistance training on muscle strength in adolescents. 27 high school students, from grade 9 to 12, volunteered into the study and were randomly divided into 3 groups: high intensity, low intensity, and low intensity with pBFR. The resistance training program included full body exercise that high intensity group trained at around 60-90%1RM and 2 low intensity groups trained at 20%1RM. Every group trained 3 times per week for 6 consecutive weeks. pBFR was performed by utilizing knee wraps of 7.6cm wide, wrapping around the proximal thigh, finally pulling the wraps to 3.0 inches overlapped end. The pBFR remained throughout the squat exercise including rest period and immediately released after training. The training volume-load was controlled throughout the experiment (total volume-load throughout the program estimate 19,675 and 22,500 and 22,500, respectively). The results showed that 1 repetition maximum parallel back squat was significantly increased in only high intensity and low intensity pBFR groups (+6.6kg and +14.2kg, respectively). However, no significant change from pre to post 1RM parallel squat in low intensity group was observed. This study demonstrated the effectiveness of pBFR that enhancing low intensity resistance training to induce increase in maximum strength and could be alternative to high intensity training.

Another pBFR technique that emerged in exercise literature was maximal cuff elasticity technique (e.g. Behringer et al. 2017; Held et al. 2019). This technique is that the elastic wrap is stretched to its maximal elasticity before wrapping around the training limbs. The protocol of application bases on the percentage of maximal length.

For example, Behringer et al. (2017) was the study that employed this maximal cuff elasticity technique with pBFR. The researchers investigated the effects of pBFR resistance training on leg muscle during sprinting training. 25 healthy male sprinters were recruited into the study and randomly assigned to sprint training program with, average age 25.6 years, or without pBFR, average age 21.7 years. The elastic knee wraps of 13cm wide were employed and it was pulled to its maximal length and marked with permanent ink at each quarter. Afterwards, the elastic wrap was applied at 75% of its maximal elasticity. This approach of application was validated by the researchers, confirming that the arterial blood flow was not completely restricted by assessing the blood flow of the posterior tibial artery at approximately 5cm proximal medial malleolus via ultrasound technique. The muscle thickness of rectus femoris and biceps femoris muscle was also investigated in this study via ultrasound technique. The exercise protocol consisted of 6 consecutive 100meter indoor sprints, with 1 minute rest interval. The results showed that after 6 weeks of training, muscle thickness of both rectus femoris and biceps femoris significantly increase from pre to post training in pBFR group (+1.5mm and +1.8mm, $p<0.05$, respectively). In the group sprinting without pBFR, muscle thinkness of both muscles only slightly non-significantly increased (+0.7 and +0.7, respectively). Besides the performance variables such as rate of force development in leg press exercise also significantly increased only in pBFR group (24.1kN/s to 30.1kN/s, $p<0.05$) while no change was observed in free blood flow group (23.4kN/s to 23.8kN/s). Furthermore, the improvement in 100meter sprint times was also only observed in pBFR group (from 12.42s to 12.5s, $p<0.05$).

Moreover, recently, Held et al. (2019) utilized pBFR by repeated the protocol of Behringer's study (2017). The variables of interest in this study were about aerobic performance and strength. 31 elite rowers, average training volumes around 18 hours/week, 8.2 years of rowing experience, were recruited to the study and randomly assigned to intervention group which trained low intensity endurance rowing with pBFR, and control group which using the same training program without the application of pBFR. The pBFR was done by using elastic knee wraps of 13cm wide, stretched to its maximal elasticity and marked with permanent ink. Then, the elastic knee wraps were applied at 75% of its maximal elasticity, exclusively used during low intensity training only. During training session, pBFR was used for two 10 minutes duration, interspersed with a 10 minutes rest interval. The pBFR training was done three times per week. The results showed after 5 weeks of training, that the percentage change in maximal oxygen consumption significantly increased in pBFR approximately 9% from pre to post training (63 to 69.7ml/min/kg but not in the control group (63.2 to 64.9ml/min/kg $p>0.05$). Besides, the significant increment in power at VO2max also observed only in pBFR training group (383 to 442, $p<0.0001$) while control group did not show significant individual power increment. This study was the first to show that inexpensive pBFR at a moderate pressure may serve as the special training method to enhance low intensity rowing performance.

From the existing literature, no matter what approach of practical blood flow restriction would be employed, the need to standardize the application during each training session was also the matter in consideration. In the real training setting such as local gym, the use of ultrasound technique in this place for confirm the occlusion from someone tightening their arms or legs with elastic knee wraps might not be practical and seem awkward.

Bell et al. (2021) highlighted a practical method for training practitioners to sense vascular occlusion before applying practical blood flow restriction (pBFR) in real training. The study involved 20 men and 15 women, with an average age of 24. Participants first visited the laboratory to measure arterial occlusion pressure (AOP) in their right legs using a handheld Doppler probe. After determining AOP, a relative pressure of 40%AOP was calculated and applied under two conditions: constrained and unconstrained.

In the constrained model, participants experienced alternating pressures of 50%AOP, 40%AOP, and 30%AOP, repeated five times with each pressure held for 3-4 seconds. In the unconstrained model, participants were directly exposed to 40%AOP by turning the pressure on and off (12:22 seconds ratio) over 11 cycles. Each condition lasted approximately six minutes.

After both conditions, participants attempted to match the 40%AOP pressure by adjusting the cuff pressure, a task repeated at 5 minutes and 24 hours post-application.

Results showed minimal error in pressure estimation, with participants in the constrained model estimating pressures close to the target (59 vs. 63mmHg at 5 minutes and 59 vs. 58mmHg at 24 hours). Similarly, in the unconstrained model, participants estimated slightly below the target (57 vs. 53mmHg and 57 vs. 54mmHg).

The study was the first to suggest that introducing participants to the target pressure may help them recognize the appropriate cuff tightness, with minimal error even after 24 hours. Given that effective pBFR pressures range from 40% to 80%AOP, this small error margin is within the effective range for eliciting muscular adaptations. ***Bell et al. (2021) recommended this method to improve the reliability of pBFR application, suggesting that participants get accustomed to the target pressure with elastic wraps before training***. It can be done by introducing the participants to the needed pressure first, and then let them get accustomed to the pressure by using elastic wraps before training takes place. To date, no study ever does this proposed technique with pBFR before. So, this approach will be proved of its effectiveness to induce muscle hypertrophy as a part of this dissertation.

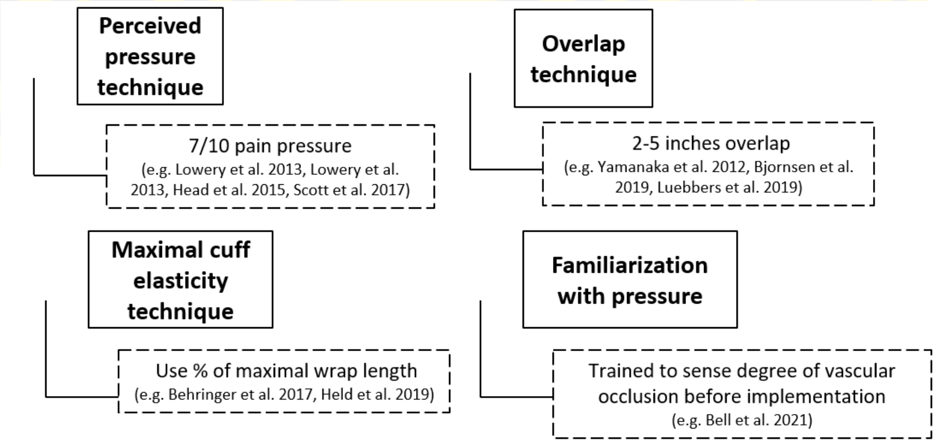


Figure 27. Methodology for applying practical blood flow restriction.

6. Cardiovascular risks from resistance training and blood flow restriction

The main concerning about blood flow restriction (BFR) technique is that the cuff has to be fastened tightly enough to partially reduce the arterial inflow and occlude the venous outflow (Rolnick & Schoenfeld, 2020); therefore, the concerning about the cardiovascular function of trainees is critical. Nakajima et al. (2006) had done a national survey in Japan about the use of BFR technique over 105 facilities where BFR training had been adopted more than 5 years. They found that until then 12,642 persons, male 45.4% and female 54.6%, utilized BFR training, and the incidence of cardiovascular side effect was very low since the reported side effects of venous thrombus, pulmonary embolism, and rhabdomyolysis were 0.055%, 0.008%, and 0.008%, respectively. Of this report, in most of the facilities, subjects had done the BFR technique around 5-30minutes each time (Nakajima et al., 2006). The safety of application of BFR is not only in concerns with normal healthy adult populations, but also with older populations. The recent meta-analysis included 12 BFR studies in participants aged over 50 years old of any gender, for total of 378 subjects (Zhang et al. 2022). Of 12 studies, 10 did the experimental exercising in lower limb muscles, with 2 studies in upper limb muscles. The cuff pressure was ranging from 120 mmHg to 100% arterial occlusion pressure. They found that low intensity (20-45%1RM) RT with BFR did not incur higher acute hemodynamic responses such as heart rate and blood pressure than high intensity RT (>65%1RM) in these population (Zhang et al. 2022).

In the study of Loenneke et al. (2011), the researchers scrutinized the effects of BFR training about the potential safety issues, suggesting that the matters of cardiovascular systems that should be concerned over the utilization of BFR included central responses of the cardiovascular system, blood coagulation, and peripheral blood flow change.

6.1 Central responses of the cardiovascular system

The first concern is central responses of cardiovascular system which was addressing about the increases in heart rate (HR) and blood pressure (BP) of trainee (Loenneke et al., 2011). In either dynamic or static exercise, it is generally accepted that the body will physiologically respond to exercising by inducing the increases in HR and BP (Kaur & Mann, 2016). HR is one of the simplest physiological responses to be measured and informative about the cardiovascular stress and strain. It is a good indicator of exercise intensity performed (Kenny, Wilmore, & Costill, 2020). For BP, it is well-documented that resistance exercise induces the acute increase in blood pressure to the higher degree compared to resting blood pressure (MacDougall, et al. 1985; Sheehan et al. 2018).

When comparing the effect of same low intensity RT (RT) with and without BFR in 11 healthy adult men, Takano et al. (2005) found that the HR, SBP, DBP, and mean arterial pressure (MAP) were slightly higher in BFR condition. They found that at the intensity of 20%1RM with knee extension exercise, the mean value of peak HR, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were 109 vs 96 bpm, 182 vs 155 mmHg, and 105 vs 99 mmHg, respectively. The MAP in BFR and non BFR condition was 127 vs 113 mmHg (Takano et al. 2005). The higher MAP, HR and SBP can indirectly indicated that the heart have to work harder during the BFR condition. This finding is supported by the recent study which found that in healthy young men, the cardiovascular system had to work more in response to BFR condition at 30% maximum voluntary contraction, compared to without BFR at the same intensity (Bazgir et al. 2016). The author critically reasoned that the heart had to forcefully eject blood against the increased MAP when using BFR condition (Bazgir, 2016). This is also true from the physiological standpoint in sport and exercise because HR and SBP are directly related to myocardial oxygen uptake and myocardial blood flow. The value is referred as rate-pressure product (RPP) which indicates the increased myocardial oxygen demand can be calculated by multiplying heart rate and systolic blood pressure (Kenny, Wilmore, & Costill, 2020). It is straightforward that the higher RPP, the higher stress on the cardiac muscle. In Bazgir's study (2016), the RPP of the group training with BFR in set 1, 2, 3, and 4 were 127.55, 119.12, 121.26, and 114.52RPP%, respectively while in the group without BFR, the values were, 102.39, 96.77, 96.07, 108.75RPP%, respectively. However, in detail, it's important to noted that in Bazgir's study (2016), they use eccentric only protocol with knee extension exercise and the findings suggested that at the end of last set the peak SBP and DBP during exercise were only slightly different, 120/84 and 127/90 mmHg in BFR and non-BFR group, respectively, but HR in BFR group is clearly higher, 94vs85 bpm. The difference in contraction mode might be an explanation of why SBP and DBP are only slightly different in Bazgir's study. While Bazgir's study employed the eccentric only exercise with isokinetic machine, Takano's study employed the dynamic mode both concentric and eccentric contraction.

Moreover, another recent study investigated the acute cardiovascular responses with the BFR at the intensity at 30% of 1 RM in twenty-four healthy participants with the plantar flexion exercise in leg press machine in sitting position (Picon et al. 2018). The researchers found that the peak average HR, SBP, and DBP were 73 bpm, 125 mmHg, 75 mmHg, respectively. The differences in acute responses between the study of Takano et al. (2005) and Pico et al. (2018) might depend on the different training protocol. While the first study employed the protocol that training for 30 repetitions in the first set and training to failure for three more sets, the later study employed the 75-repetition protocol (30, 15, 15, 15 repetitions, with 60-seconds rest between sets). The higher in repetition and duration in the first study might be the factors that influenced the cardiovascular responses to a higher degree. Besides, the knee extension exercise in Tanako's (2005) study involved quadriceps muscles which are anatomically a lot larger than the gastrocnemius muscles that were trained in Picon's study (2018). Therefore, less blood flow needed to small muscle might contribute to lower myocardial workload and lower central cardiovascular responses. This logic was supported by the study of Frank and McLean (2000) who found that when comparing between isometric contraction at 20% maximal voluntary contraction for 5 minutes between quadriceps (large) muscles and forearms (small) muscles, the cardiovascular response, heart rate, was higher in quadriceps than forearms condition, approximately 95 vs 75 bpm, respectively.

However, when compare to the general resistance exercise going along with the recommendation of ACSM at 70-100%1RM (Ratamess et al. 2009) or NSCA at 67-85%1RM (Brown, 2017), it seems that the central responses of cardiovascular system in low load either with or without BFR are lower or at least not different. According to the classic study of acute blood pressure response to heavy resistance exercise by MacDougall et al. (1985), the results showed that in healthy men, training at 95% of RM in leg press exercise to failure could result in highest absolute pressures of 320/250 mmHg, with the maximum heart rate over the time of exercise touched 166 bpm and the average mean blood pressure was around 131 mmHg. Surprisingly, the blood pressures in one subject exceeded 480/350 mmHg in this study in double leg press. Furthermore, they found that the exercise that involved more muscles results in higher peak SBP and DBP as they compare arm curls and leg press (MacDougall et al. 1985). Nonetheless, the later finding seemed to be in contrast with the study by Assuncao et al. (2007) which compared the cardiovascular response in healthy men via strength training at the intensity of 10 repetition maximum (RM), corresponding to approximately 75%1RM between large group of muscle and small group of muscle. The results showed that the both high intensity exercises induced the increase in HR and BP to the similar higher degree. In extensor bench exercise which involves the hip extensor muscles, the peak HR, SBP, and DBP were 117 bpm, 156 mmHg, and 75 mmHg, respectively while for biceps curl at 10RM, the value were, 124 bpm, 152 mmHg, and 72 mmHg, respectively. They concluded that the size of the involved muscle mass would not influence in the acute cardiovascular responses (Assuncao et al. 2007). Pedreiro et al. (2016) later supported this hypothesis that they found no differences in acute central response to exercise involved either large or small muscle group. The researcher compared 3 sets of 10 repetition maximum of elbow flexion (biceps muscles) and knee extension (quadriceps muscles) exercises and found that there were no significant differences in HR, SBP, and DBP during all 3 sets of exercises.

Another study of acute cardiovascular response to leg press and heel raise exercises had been investigated (Downs et al. 2014). The researchers recruited 13 moderately active healthy participants, average age 31.8 years into the study. The participants performed 3 sets to failure of unilateral leg press and heel raise under random conditions: HL (80%1RM) or BFR (20%1RM). The BFR conditions performed leg press at load around 10.9kg and 16.7kg for heel raise. The HL performed 40.4kg and 68.7kg for leg press and heel raise, respectively. The acute cardiovascular response showed that the HR and SBP increased in all groups from pre to post exercise significantly ($p < 0.05$). The HR of HL increased from 69 to 113bpm post exercise and BFR increased from 72-75 to 99-100bpm. The SBP of HL increased from 115 to 135 mmHg and BFR increased from 114-118 to 140-156 mmHg. Interestingly the stroke volume only increased significantly from baseline in only HL group (62.1 to 70.1 mL). That the BFR conditions did not increase the stroke volume might be because the restriction of the cuff reduced the venous return that finally resulted in a decrease in the cardiac preload or it was possible that the restriction of the cuff would increase the vascular resistance and afterload (MacDougall & Sale 2014).

In agreement with Downs' study, Poton and Polito (2014) found that low load BFR RT elicited similar responses in HR, SBP, and DBP compared to high load RT. The participants included 12 healthy trained men and all participants randomly underwent different training conditions on different days: high intensity (80%1RM) and low intensity BFR (20%1RM). The exercises consisted of 3 sets of knee extension at identified intensity. The training load was average 14.5kg for low intensity BFR and 58.5kg for high intensity. The hemodynamic results showed that both groups presented significantly increase in SBP, DBP, and HR, ($p < 0.05$) in comparison to rest. The peak HR in high intensity and low intensity BFR was around 135 and 120bpm, respectively. The peak SBP was around 190mmHg in both groups, and the peak DBP was 125 and 115mmHg, respectively. However, when comparing set by set, the resulted demonstrated that at set 1st and 2nd, the low intensity BFR RT had lower SBP, HR in relation to high intensity training while DBP was lower in all 3 sets. The finding suggested that the high magnitude of intensity may be the main factor that provoked the higher hemodynamic increase during training (Poton and Polito 2014).

From another recent study in healthy subjects, Moreira et al. (2017) suggested that the cardiovascular response to strength training is directly and linearly affected by intensity. The study showed that the increases in acute heart rate and blood pressure linearly related with increased intensity. They compared training at 3 different protocols: 4 repetitions at 90%1RM, 8 repetitions at 80%1RM, and 15 repetitions at 60%1RM, and the results showed that the post exercise HR, SBP, and DBP changed from 66 to 123bpm, 119 to 148mmHg, and 78 to 85mmHg, respectively at intensity 90%, from 67 to 118bpm, 119 to 144mmHg, and 77 to 82mmHg, respectively at intensity 85%, and from 66 to 111bpm, 118 to 138mmHg, and 78 to 81mmHg, respectively at intensity 65% (Moreira et al. 2017). This study importantly suggested that the training volume, high numbers of repetitions, was not always the determinant of cardiovascular response compared to training intensity, high%1RM, because the subjects trained a lot less repetition in high intensity protocol than moderate intensity protocol (4 vs 15 repetitions). This finding was corresponding to previous discussion by Poton and Polito (2014). In the BFR training point of view, that usually comes along with low intensity and high repetitions in a single set, this consequently suggests that it is not necessary that the high number of repetition should be concerned when considering central response of cardiovascular system since the training intensity is so low and the number of repetition is not always a determinant of blood pressure (e.g. Hughes et al. 2018).

Neto et al. (2014) investigated the acute effects of exercising biceps curl, triceps extension, knee extension, and knee flexion on different training protocols. 24 normotensive healthy trained men, average age 21 years, visited the laboratory and randomly performed one of three training protocols: high intensity 80%1RM 4 sets of 8 repetitions, low intensity 20%1RM or low intensity 20%1RM BFR 1 set of 30 repetitions followed by 3 sets of 15 repetitions. The findings showed that there was a significant increase in HR from baseline versus immediately post exercise ($p < 0.05$). The peak HR in high intensity, low intensity and low intensity BFR was ~115, ~115, and ~120bpm, respectively. However, it was interesting that the RPP was increased in both high intensity and low intensity BFR protocol to the similar degree, 71.8% vs 75.3%, respectively (Neto et al. 2014). This was indicative that both high intensity and low intensity BFR induced the increase in myocardial oxygen demand to the similar degree (Schutte et al. 2013).

However, the literature about the volume and intensity over the blood pressure is still conflicted. A recent study had also demonstrated that the cardiovascular response was higher in the group training at higher volume and lower intensity. Gjovaag et al. (2016) compared the acute responses in SBP and DBP in thirteen healthy men between the protocol 89%1RM and 48%1RM. The results showed that the SBP and DBP increased up to 203 mmHg and 126 mmHg, respectively in 48%1RM group while the values increased up to 154 mmHg and 99mmHg, respectively in 89%1RM group. Besides, the MAP increased significantly to 165 and 127 mmHg in 48% and 89%1RM respectively. The peak HR was 124 bpm for 89%1RM and 150 bpm for 48%1RM. The total number of repetition for 89%1RM was 4 while the repetition for 48%1RM was 20. Further research is needed to draw the conclusive argument. Anyway from the practical standpoint, when comparing to the RT with BFR, the intensity in this study in still much higher (48%1RM) if compared to the standard recommended BFR protocol (20-30%1RM) (Krzysztofik et al. 2019); therefore, the results might be different in investigate in BFR condition with lower intensity. One study existed to support this rationale. Hughes et al. (2018) compared the blood pressure response between low intensity 30%1RM with BFR training and 70%1RM training and found that SBP and DBP post exercise were 129 vs 139 mmHg and 78 vs 82mmHg, respectively. The total number of repetition performed in BFR group and 70%1RM group was 75 and 30, respectively. This study showed that the higher volume in repetitions, still, does not differ in blood pressure which was in contrast with Gjovaag's study (2016). In the same way, the very recent study investigated the high intensity RT with different speed on the blood pressure with different repetition volume. Apkarian (2019) conducted a study with eighteen healthy subjects performing leg press at around 70%1RM. For SLOW group, they performed 3 sets of 6 seconds per repetition or 10 repetitions per minute. The FAST group, they performed same 3 sets of 2 seconds per repetition or 30 repetitions per minute. The results showed that the acute peak HR, SBP, and DBP for both group were not different, measuring either at rest, end set 1, end set 2, and end set 3. Peak HR in FAST was 116-118 bpm while peak HR in SLOW was 112-119 bpm. Peak SBP in FAST was 112-127 mmHg while Peak SBP in SLOW was 112-132 mmHg. And peak DBP in FAST was 63-69 mmHg while Peak SBP in SLOW was 62-66 mmHg (Apkarian 2019). This study manifested that higher number of repetitions when equated by time did not necessarily result in higher cardiovascular response.

Besides in the chronic state, a study also demonstrated that high load RT and low load BFR results in the same central responses. Fahs et al. (2012) investigated the effect of training with integrative mixed loading and chronic adaptation. All participants perform 3 sets of 10 repetitions of each exercise at 50% 1RM including lat pulldown, seated shoulder press, elbow extension, elbow flexion and then each group trained according to their conditions, with high load performing 70%1RM and low load BFR performing 20%1RM for 3 sets of knee extension and knee flexion exercises. After 6 weeks, the results found that there was a slight decrease, but not significant, from pre to post in both groups high load and low load BFR in SBP (120 to 119 and 127 to 121 mmHg), mean arterial pressure (86 to 83 and 90 to 85 mmHg), and heart rate (62 to 59 bpm and 61 to 62 bpm) respectively (Fahs et al. 2012). In the same way, Yasuda et al. (2014) reported the decrease in SBP after 12 weeks of BFR RT. The finding suggested that the group training with BFR technique significantly ($p < 0.05$) reduced the SBP from pre to post (151 to 142mmHg). The HR and DBP maintained the same value between pre to post training (Yasuda et al. 2014).

Importantly, a recent systematic review and meta-analysis by Domingos and Polito (2018) provided a conclusive remark that when comparing the blood pressure response between the traditional resistance exercise and BFR resistance exercise, the results concluded from 17 eligible studies that RT with BFR did not elicit the significant difference in SBP when compared to traditional resistance exercise at the intensity more than 60%1RM. However, when compared to traditional resistance exercise at the intensity lower than 60%1RM, it showed the slightly higher values of SBP and DBP in BFR condition. In agreement with the previous mention study, Zhang et al. (2022) found that in meta-analysis of older adult aged over 50 years, it was undeniable that low intensity BFR caused the higher rise in HR SPB and DPB than low intensity without occlusion. However, the level of increases was not significantly different when compared to higher intensity, more than 60%1RM, and when full recovery, there was no significant difference in resting hemodynamic response compared with regular RT.

From all existing evidences, it is appealing to infer that the central response of cardiovascular system from low intensity BFR training is not significantly different from (or worse than) high intensity when considering HR, SBP, DBP. Therefore, from the central cardiovascular response standpoint, BFR should be a safe alternative and optional in RT protocol for practitioners of interest.

Table 5. Acute and chronic effect of LRT-BRT compared to LRT or HRT on central hemodynamic responses

Study	**Duration**	**Subjects**	**Intensity**	**Training protocol**	**Contraction mode & Exericse**	**Main outcome**
Tanako et al. 2005	Acute	11 healthy young men	20%1RM	LRT-BFR LRT	Dynamic Knee extension	Average peak HR, SBP, and DBP were 109 vs 96bpm, 182 vs 155 mmHg, and 105 vs 99 mmHg, in the BFR and non-BFR group, respectively.

Bazgir et al. 2016	Acute	16 healthy young men	30%MVC	LRT-BFR LRT	Eccentric-only knee extension	Average peak SBP/DBP were, 120/84 and 127/90 mmHg in the BFR and non-BFR group, respectively,
Picon et al. 2018	Acute	24 healthy young men	30%1RM	LRT-BFR	Dynamic plantar flexion	Average peak HR, SBP, and DBP were 73bpm, 125mmHg, 75mmHg, respectively.
MacDougall et al. 1985	Acute	5 healthy young men	95%1RM	HRT	1)Dynamic leg press 2)Dynamic arm curl	The highest absolute SBP/DBP, HR, and MAP were 320/250mmHg, 166bpm, 131mmHg, respectively.
Assuncao et al. 2007	Acute	18 Healthy young men	75%1RM	HRT-large muscle HRT-small muscle	1)Dynamic hip thrust 2)Dynamic bicep curl	Both high-intensity exercises induced an increase in HR and BP to a similar degree.
Pedreiro et al. 2016	Acute	8 Healthy middle-age women	10RM	HRT-large muscle HRT-small muscle	1)Dynamic elbow flexion 2)Dynamic knee extension	No differences in the acute central response, regardless of the muscle size.
Downs et al. 2014	Acute	5 healthy young men and 8 healthy	20%1RM 80%1RM	LRT-BFR HRT	1)Dynamic unilateral leg press 2)Dynamic heel raise	Similar increase of average peak HR from 69 to 113bpm and from72-75 to 99-100, in HRT and LRT-BFR group, respectively.

		young women				Similar increase of average peak SBP from 115 to 135mmHg and from114-118 to 140-156, in HRT and LRT-BFR group, respectively.
Poton & Polito 2014	Acute	12 healthy young men	20%1RM 80%1RM	LRT-BFR HRT	Dynamic knee extension	The peak HR in HRT and LRT-BFR were approximately 135 bpm and 120 bpm, respectively. The peak SBP was approximately 190 mmHg The peak DBP was 125 mmHg and 115 mmHg in HRT and LRT-BFR, respectively
Moreira et al. 2017	Acute	15 healthy young men	65%1RM 80%1RM 90%1RM	HRT	Dynamic bench press	Peak HR and SBP were 123bpm/148mmHg, 118bpm/144mmHg, and 118bpm/138mmHg, in 90%1RM, 80%1RM and 60%1RM protocols respectively.
Neto et al. 2014	Acute	24 healthy young men	20%1RM 80%1RM	LRT LRT-BFT HRT	1)Dynamic biceps curl 2)Dynamic triceps extension 3)Dynamic knee extension	The peak HR observed in the HRT, LRT, and LRT-BFR protocols were approximately

					4)Dynamic knee flexion	115bpm, 115bpm, and 120bpm respectively.
Gjovaag et al. 2016	Acute	13 healthy young men	48%1RM 89%1RM	LRT HRT	Dynamic knee extension	The peak SBP and HR was 203mmHg/150bpm and 154mmHg/124bpm in LRT and HRT, respectively.
Apkarian 2019	Acute	18 healthy young men	70%1RM	HRT fast HRT slow	Dynamic leg press	When equated by time under tension, no significant difference in peak HR, SBP, and DBP.
Fahs et al. 2011	6 weeks	11 healthy young men	20%1RM 70%1RM	LRT-BFT HRT	1)Dynamic knee extension 2)Dynamic knee flexion	Similar decrease in resting HR, SBP, MAP in both group.
Yasuda et al. 2014	12 weeks	21 healthy older men and women	20-30%1RM	LRT-BFR	1)Dynamic knee extension 2)Dynamic leg press	Significantly reduced SBP from pre to post-training, 151 to 142mmHg.

6.2 Blood coagulation

The second concern about the effect of applying BFR on vascular system was blood coagulation (Loenneke et al. 2011). It is well-known that the human body must maintain the homeostasis to keep every single process inside the body to work properly. One process that must be maintained throughout called "heamostasis". Heamostasis is the physiological process to stop bleeding at injured side of blood vessel and has the blood circulation continued (Gale, 2010). It is the delicate manipulation between the two main components including coagulation process, which the platelets are activated and adhering to the side of injury and the fibrinolytic process, which limits the undue extension of the fibrin clot (Stefani 1954). Studies suggest that regular RT and exercise can influence the heamostasis by balancing the regulation between blood coagulation and fibrinolytic activities in both healthy populations and patients with diseases (El-Sayed 2004; Dejong et al. 2006; Nascimento et al. 2012).

The study by Vanwye et al. (2017) had mentioned the concern over the thrombus formation during utilization of BFR technique that the data from two surveys of nearly thirteen thousand practitioners who used BFR training reported that the incidence of deep vein thrombosis, a blood clot in a vein located deep inside the body, was less than 0.06% and pulmonary embolism, a blockage in one of the pulmonary arteries in lungs, was less than 0.01%. In agreement with a previous survey in Japan by Nakajuma et al. (2006), BFR training had been utilized with 5,311 athletes, 2,776 orthopedic patients, 5,382 older adults, and 15,284 healthy people. The report of venous thrombus was observed only in 7 cases and pulmonary embolism was observed in only 1 case.

From the latest literature, the very recent systematic review of randomized and non-randomized trials by Nascimento et al. (2019) reported the short and long term effect of BFR training on blood heamostasis. They mentioned that from nine studies, a total of 127 participants, which were eligible for data extraction, the results suggested that a short-term intervention of training with BFR increased the activity of fibrinolysis when measured through blood testing protein, tissue plasminogen activator (tPA). In a previous study, it had been showed that the acute bout of RT in middle-age patients with the coronary artery diseases, performing 8 exercises for 1 set of 10 repetitions each, resulted in the increase of tPA and decrease in plasminogen activator inhibitor-1 (PAI-1)(Dejong et al. 2006). Since a tPA is a protein that functions to dissolve the blood clots (Jilani & Siddiqui 2020) and a PAI-1 is inhibitors of the plasma fibrinolytic activity (Cesari, Pahor, & Incalzi 2010). Consequently, the increase in tPA and decrease in PAI-1 resulted in the lower risk of thrombus formation. Moreover, a previous study by

Nakajima et al. (2007) investigated the fibrinolytic and coagulation responses after the implementation of BFR RT for 4 sets (1 set of 30 repetitions and 3 sets of 15 repetitions) at the intensity of 30% 1RM, demonstrating that the training did not affect the intravascular blood clot formation since they reported there was no change in blood coagulation parameters: prothrombin time (PT), thrombin time (TT), factor 8, and factor 10 , after exercising leg press in healthy subjects. Furthermore, although the blood markers that reflected the activity of coagulation cascade and platelet aggregation did not change significantly, the level of tPA increased significantly ($p < 0.05$) after training (Nakajima et al. 2007). The finding was supported by another study which found the increase in tPA after RT with BFR. Clark et al. (2011) investigated the effect of leg press exercise with BFR at 30% 1RM and found the huge 30-40% increase of tPA immediately after training. They discussed that it was difficult to conclude if the increase in tPA was the result of vascular compression, RT, or the combination of the two because it had been known that vascular compression alone without RT was able to stimulate the fibrinolytic activity (Holemans, 1963) as well as RT. Nevertheless, no matter what was the cause of increase tPA, it seemed that BFR RT was beneficial for inducing fibrinolytic process.

For the long-term effect of BFR training, the systematic data found no significant changes in blood clotting function in healthy subjects who trained with low load RT with BFR (Nascimento et al. 2019). This is supported by previous study by Clark et al. (2011). The researchers compared the effect of 4 weeks RT with BFR (30%1RM) and high load RT (80%1RM) on the blood makers that reflects vascular function in healthy young subject, age 18-30 year. The participants in the BFR RT group performed 3 sets of approximately 30-50 repetitions per set while the participants in high load RT performed 3 sets of 8-12 heavy repetitions per set. They found that no significant changes in D-dimer protein after training in both groups (Clark et al. 2011). D-dimer is a protein that presents in blood circulation after the blood clot is dissolved by fibrinolytic pathway; therefore, the unchanged level of D-dimer means there is no clotting disorder.

Besides, A study by Fry et al. (2010) investigated the effect of 20% 1RM BFR RT in the healthy older men, average age 70 years old, with 4 sets of leg extension exercise (1 set of 30repetitions and 3 sets of 15 repetitions). They did the blood analysis for monitoring the potential risk of deep vein thrombosis from exercise with D-dimer concentrations test before and after exercise and found the D-dimer values were 0.37ug/ml and 0.39ug/ml, respective, statistically not significant difference between the values (Fry et al. 2010). The result of Fry's study (2010) was repeated in order to investigate the result in different population by Madarame et al. (2010). The later study was to investigate the effect of BFR RT on coagulation system in healthy young subject, average age 25 years old. The participants perform leg extension exercise at 30% 1RM for the same repetition protocol with Fry's study. The blood samples were taken at pre-test and 10 minutes, 1, 4, and 24 hours post exercise. The results showed that plasma volume significantly reduced after BFR exercising, -4.6%, compared to without BFR. However, the blood markers of thrombin generation, thrombin-antithrombin III complex (TAT) and intravascular clot formation, fibrin degradation product (FDP) were not observed increasingly after 4 sets of BFR RT. Besides, the values of D-dimer did not change significantly post-exercise either at 10min, 1, 4, and 24 hours. The researchers suggested that low intensity training with BFR did not negatively affect the coagulation system in healthy young subjects (Madarame et al. 2010).

Afterwards, the study by Madarame et al. (2013) investigated the effect of RT with and without BFR at 20%1RM for 4 sets, albeit done with patients of average age 57 years with ischemic heart disease. Blood sample analysis showed that D-dimer value increased only slightly after exercising (0.04 to 0.10ug/ml). The researchers discussed that although the level of D-dimer concentrate post-exercise was slightly higher than pre-exercise in both conditions, this increase was unlikely the result of intravascular clot formation because after the statistic correction was done, the increase was no longer observed. Besides, the D-dimer observed in this study was still in the clinically normal range; therefore, the low intensity RT either with or without BFR should not affect the plasma D-dimer concentration and causes blood coagulation in patient with ischemic heart disease (Madarame et al. 2013). Besides, the interpretation of this finding should be careful and could not be assumed for healthy subjects or other groups of population.

A year later, a study by Yasuda et al. (2014) examined the effect of BFR RT in healthy older adult, age between 61-84 years, on the muscle size and arterial functions. After 12 weeks of RT at 20% 1RM on knee extension and leg press exercises, the results showed that the muscle cross sectional areas of quadriceps, adductors, and gluteus maximus increased up to 8.0%, 6.5%, and 4.4%, respectively. The average increase of hypertrophic potential was 0.33% per session. Interestingly, the training did not negatively affect the arterial functions in these subjects for there was no statistically significant change in D-dimer concentration between pre and post training (0.5 to 1.2) (Yasuda et al. 2014). In the next year, the Yasuda's study was repeated again with different training protocol. A study examined the effect of elastic band RT with and without BFR in the healthy older adult, age 61-85 years (Yasuda et al. 2015). The training protocol was to train with elastic band by performing arm curls and triceps press down for 4 sets of total 75 repetitions. The hypertrophic response of muscle size and arterial functions were measured pre and post 12 weeks intervention. The results showed that the group training with elastic band resistance exercise without BFR was not significantly observed the hypertrophic response, while the group training with BFR produced the hypertrophic response of elbow flexor muscle cross sectional areas of 0.73% per session. However, the level of D-dimer concentration did not change between pre and post intervention in both groups (0.2 to 0.3 and 0.2 to 0.3) (Yasuda et al. 2015). For gender difference, Yasuda et al. (2015) also investigated the effect of elastic band RT with BFR in healthy older women as well. The group of healthy older women age from 61-84 years old participated in the study on 12 weeks intervention with and without BFR. The study found that after intervention finished, the muscle cross sectional areas of elbow flexor and elbow extensor muscles increased significantly only in group training with BFR. Nonetheless, the marker of blood coagulation, D-dimer, did not change from pre to post in both group (0.21 to 0.25 with BFR and 0.25 to 0.25 without BFR). Appealingly, the follow-up recheck of blood marker, D-dimer after 12 week detraining still found the value of D-dimer unchanged in both with and without BFR groups (0.26 and 0.27, respectively) (Yasuda et al. 2015). From three mentioned Yasuda's study, literature has showed the safety of BFR on both healthy older men and women. They can employ both RT and elastic band RT program to increase muscle mass with no effect on blood D-dimer concentrations.

Other blood markers, which had ever been investigated in RT with BFR, indicating the risk of thromboembolism include prothrombin time (PT) – the time in seconds how long that the plasma will coagulate after addition of calcium and important activator, thromboplastin (Kamal, et al. 2007), fibrin degradation products (FDP) – the substance which remains in blood circulation of the clot is dissolved (Gentry et al. 2008), thrombin-antithrombin III complex (TAT), – high TAT indicating the high thrombin level in hypercoagulable state (Matsuo, Kario, & Matsuto 1991), fibrinogen, factor 8, and factor 10 (Nakajima et al. 2007; Loenneke 2011). Loenneke et al. (2011) summarized that from few studies that investigated the effect of BFR RT with these markers, the results showed that no significant change observed in these markers. From the existing evidence, the aforementioned literature suggested that low-intensity blood flow restriction exercise did not increase the risk of coagulation activity, reference by D-dimer value. In contrast, the fibrinolytic activity, tPA value, appeared to be enhanced with RT with blood flow restriction.

6.3 Changes of blood flow after exercise

Last but not least, while applying the BFR technique, the consideration about the blood flow changes post-exercise (Loenneke et al. 2011) should be in concern. The concern arose from the rationale that the BFR RT needed to utilize the manipulation of the restriction of the blood vessels of working muscle, there came time for cardiovascular responses that would either congest or distend the arteries and veins when tightening or loosening the cuff. Therefore, these changes in the blood flow post-exercise must be monitored when applied BFR to the practitioners because some risk might be, in theory, enlarged, such as the potential of the valvular system damage after releasing the cuff (Kelly et al. 2020). For example, Patterson and Furguson (2010) examined the response of post-occlusive blood flow change of calf muscle after unilateral plantar-flexion resistance exercise. The participants included 16 young healthy women, assigned to perform RT at 25%1RM and 50%1RM with BFR on dominant limb. The occlusion duration lasted around 5-8 minutes per session. The results showed that both intensity 25%1RM and 50%1RM with restricted condition, the post-occlusive blood flow change significantly increased ($p < 0.05$) from 19.8 to 27.4 ml/min/100 ml and from 20.3 to 29.9 ml/min/100 ml, respectively while the limb with non-restricted condition at both intensity did not significantly increase post-occlusive blood flow (20.3 to 21.4 ml/min/100 ml and 23.0 to 24.1 ml/min/100 ml). Literature is well-documented about the mechanism of BFR that this type of RT can induce the metabolic stress to the higher degree compared to without occlusion (e.g. Loenneke, Wilson, & Wilson 2009; Pearson & Hussain 2014; Jessee M et al. 2018). Therefore, this increase in post-occlusive blood flow might partially be attributed to more accumulations of these metabolites during contraction in hypoxic condition due to the fact that metabolites, such as adenosine (Sato et al. 2005), lactic acid (Lande & Whelan 1962), inorganic phosphate (Hilton 1977), and hydrogen ion (Charter et al. 2016), possess the vasoactive characteristics. Hence, the accumulation of metabolites and change in post exercise blood flow from application of BFR must inevitably be in the practitioners' concern.

In research setting, the direct evaluation of vascular function in human body is impossible. However, Horiuchi and Okita (2012) suggested some of the indirect alternative non-invasive methodologies to investigate the impact of BFR RT on vascular function.

6.3.1 Arterial compliance and stiffness

The first method is to consider arterial compliance and stiffness (Horiuchi & Okita 2012). The arterial compliance is a biomechanical property of the arterial wall, defining the ability to distend and increase the volume (Papaioannou et al. 2014), while the arterial stiffness, in contrast, defines the rigidity of the arterial wall (Cheung 2010). In literature, numbers of studies have showed that the degree of arterial compliance declines with age. For example, a study by Tanaka, DeSouza and Seals (1998) reported the significant age-related increase in central arterial stiffness in sedentary healthy females. Furthermore, over the last 30 years, many studies suggested monitoring the increase in arterial stiffness or decrease in arterial compliance as the potential risk factors of cardiovascular disease (Arnett et al. 1994; Hodes et al. 1995; Mattace-Raso et al. 2006; Vlachopoulos et al. 2015, Lee & Joo 2018).

When considering application of BFR, many studies investigated the effect of training and arterial compliance and stiffness as well. Kim et al. (2009) were the very early group of researchers who investigated the effect of BFR RT on arterial compliance. The study was conducted with 30 healthy men age between 18-35 years. The experiments included a group of 10 of low intensity BFR RT 20%1RM, the high intensity RT 80%1RM, and BFR only with no training. Both training group trained around 20-30 minutes per day for 3 days per week for 3 weeks. The exercises consisted of 2 sets of 10 reps of each exercise: leg press, knee extension, and knee flexion. The results about arterial compliance showed that the percent changes in arterial compliance and cardiovascular variables after training were not significant difference among groups. Although not reaching statistically significant, the in depth analysis showed that BFR RT increased the large arterial compliance index by average 17.9% while the traditional high load RT showed a slight increase only 1.4%. In contrast, the increase of

1.4% of small arterial compliance index in BFR RT group while the traditional high load RT experience a decrease of 6.41% (Kim et al. 2009). The result of a slight decrease in arterial compliance in high load RT was in accordance with some previous studies (Miyachi et al. 2004; Collier et al. 2008). Miyachi et al. (2004) reported the unfavorable chronic effect of high load 80%1RM RT with the reduction of the central arterial compliance by 19% and the increase of arterial stiffness by 21% after 4 month of training. Similarly, Collier et al. (2008) found that after 4 weeks, the group training with high intensity RT (65%1RM) significantly increased arterial stiffness ($p = 0.0001$) both in the elastic central arteries (14.5%) and in the peripheral muscular arteries (8.7%). However, Kim et al. (2009) concluded that in this study both large and small arterial compliance were not significantly negatively affected by the either the BFR or traditional high intensity RT.

In fact, there are many other studies until recently which suggest that high intensity RT reduces the arterial compliance after training. For example, Tagawa et al. (2018) investigated the RT with high load 75%1RM for 5 sets of 10 repetitions, 3 times per week, in 14 healthy male subjects. The results show that although the values of SBP, DBP and HR remained unchanged, the arterial compliance measured by carotid artery echography of the experimental group significantly decreased around 13% ($p < 0.05$) after 4 weeks of biceps curl. (Tagawa et al. 2018). The researcher proposed that the decrease in arterial compliance in this study might occur due to the increase in local vasoconstrictive peptide, Endothelia-1 (ET-1) around the vessels. ET-1 was an extremely powerful vasoconstrictor (Houde et al. 2016); therefore, over the course of training, repeatedly stimulating of local ET-1 might possibly contribute to the increase in arterial stiffness in the long-term (Tagawa et al. 2018).

Until now, there are 2 mostly cited meta-analyses about the effect of RT on arterial stiffness in healthy subjects (Miyachi 2013; Ceciliato et al. 2020). First, the meta-analysis by Miyachi (2013) concluded from 8 randomized controlled trials studies, 193 subjects, and the results showed high intensity RT was significantly associated with an increase in stiffness of 11.6%. It is important to note that the high intensity RT in Miyachi's meta-analysis had the cut-off point of intensity at around 80%; therefore, this can not be generalized for lower intensity as well as BFR RT because no association was found between increase in stiffness and moderate intensity in this meta-analysis (Miyachi 2013). And very recently, Ceciliato et al. (2020) repeated the meta-analysis over the effect of RT on arterial stiffness again. They found that from total 10 studies, 310 subjects included, the results showed that RT did not affect (improve or worsen) the arterial stiffness in healthy subjects. However, it must be additionally mentioned that the data used in this study included the various intensity of RT from 20% to 90%1RM, and they did not stratify the intensity when analyzing as same as Miyachi's study did. Accordingly, the researcher reported very high heterogeneity of the data (I2 = 91%; p < 0.01). Therefore, the results should be interpreted with caution that RT did not affect vascular function.

The next study about BFR RT by Fahs et al. (2011) examined the acute effect of different training intensity on acute vascular responses in 11 young male subjects, average age 25 years. The randomized cross-over design was utilized. The RT regimens included high intensity at 70%1RM for 3 sets of 10 repetitions, low intensity with and without BFR at 20%1RM for 1 set of 30 repetitions and 3 sets of 15 repetitions. The total time for each session was around 18 minutes for 4 exercises: supine leg press, seated knee flexion, seated knee extension, and seated plantar flexion machine. The results found although there was no significant difference in SBP, DBP from pre training to 15 and 45 minutes post training, the large artery elasticity index increased at 15 minutes post training but returning to baseline after 45 minutes post training in all group. The researcher concluded that both traditional high load and low load either with or without BFR resulted in similar acute post-exercise increases in large arterial compliance (Fahs et al. 2011). This is worthy of notice that the acute increase in arterial compliance from high intensity training of Fahs' study (2011) was in contrast with the aforementioned studies (Miyachi et al. 2004; Tagawa et al. 2018) which showed that high load RT reduce arterial compliance in chronic adaptation. Therefore the time course of measurement can be another important variable when considering investigating the arterial compliance.

A year later, Fahs et al. (2012) again compared the vascular effects of low load BFR, moderate load, high load RT, and control group. This was randomized controlled trial study design. The participants in this study were 41 healthy young men, average age of 21 years. The RT protocols, knee extension and knee flexion exercises, were performed 3 times per week for 6 weeks. The high load group (HL) performed 3 sets of 10 repetitions at 70%1RM, the moderate load group (ML) performed 3 sets of 15 repetitions at 45%1RM, and the low load BFR group (BFR) performed 1 set of 30 repetitions and 3 sets of 15 repetitions at 30%1RM. The results found that there was no significant difference from pre to post in large artery elasticity index (21 to 19.4, 20.5 to 18.1, and 19.4 to 20.4 ml/mmHg) and small artery elasticity index (11.1 to 10.5, 8.2, 9.2, and 8.7 to 9.9 ml/mmHg) in all group, HL, ML, BFR respectively. The researcher concluded that when measured in chronic state, none of the RT regimens in this study did negatively affect the arterial compliance (Fahs et al. 2012).

In 2014, Yasuda et al. investigated the effect of BFR RT in older adults on arterial stiffness. 21 participants age 61-84 years in healthy status performed leg press and knee extension exercises at 20-30%1RM with BFR for 4 sets of 75repetition protocol with 30 seconds rest between set with frequency of 2 days per week. The results found that the arterial stiffness was maintained (90 to 91 m/sec) after 12 weeks of training (Yasuda et al. 2014). The Yasuda's finding was duplicated when investigated in the younger subjects that the arterial compliance was likely to be maintained or unaffected when training at low intensity with BFR. Ozaki's study (2012) investigated the effect of high intensity and low intensity BFR RT in 19 young men. The intensity performed was 75%1RM, 3 sets of 10 repetitions, and 30%1RM, 4 sets of 75 repetitions protocol, respectively. After training with flat bench press exercise for 3 days per week for 6 weeks, the results showed that there was no change in resting carotid systolic arterial pressure and brachial systolic arterial pressure from pre to post in both group. However, the carotid arterial compliance was significantly decreased in high intensity group training at 75%1RM (0.14 to 0.11mm2/mmHg), and slightly increase in low intensity BFR RT training at 30%1RM (0.15 to 0.17mm2/mmHg). Ozaki et al. (2012) discussed that the decrease in central arterial compliance was correlated with elevations of systolic arterial pressure during training session because the systolic arterial pressure reached 188mmHg in high intensity RT while just 160mmHg in low intensity BFR RT. Therefore, magnitude of changes in blood pressure responses during workout might be the influencing factor for RT-induced decrease in arterial compliance that the increase in systolic blood pressure over 190 mmHg during an exercise session may produce the unfavorable effect on arterial compliance in high intensity group (Ozaki et al. 2012).

Moreover, Yan et al. (2018) recently investigated the effect of cardiovascular function with low intensity training in 24 healthy men. The training protocol included performing 5 bouts of 1 minute of elbow flexion exercise at 30%1RM with BFR, for 5 times per week. The result showed there appeared the chronic adaptation of significant increase in aortic arterial compliance ($p < 0.05$), and a decrease in the systolic blood pressure at rest after 8 weeks of training. The researcher suggested that BFR RT could have the positive effect on blood pressure and with BFR technique, there showed the positive influence on cardiac pump function, increasing in ejection fraction, fractional shortening, and stroke volume (Yan et al. 2018).

Few study also investigated the vascular compliance from aerobic training with BFR. Ozaki et al. (2010) studied the effect of 20 minutes walking at intensity 45% of heart rate reserve, 4 days per week in sedentary men and women, aged 57 to 76 years. The restriction cuff was applied at the upper tights during walking. Arterial compliance was measured via carotid arterial compliance. The finding demonstrated that the maximum isokinetic knee extension and flexion strength and muscle size significantly increased

($p < 0.01$) after 10 weeks of training (8.7%, 15.0%, 3.2%, respectively). Besides, the improvement in arterial compliance was also observed, from 0.084 to 0.118 ($p < 0.01$). One possible explanation of walking with BFR inducing arterial compliance might be because aerobic exercise did not cause the increase in blood pressure as high as when compared to heavy resistance exercise. Since it was reported that RT induced the arterial stiffness was related to the elevation of extremely high blood pressure during exercise bout (MacDougall et al. 1985; Ozaki et al. 2012). Another study, by Iida et al. (2011), investigated the effect of walking with BFR on venous compliance. The study examined the 6 weeks effect of slow walking on treadmill, 20 minutes per day for 5 days per week, in 16 elderly women age from 59-78 years. The chronic adaptation revealed that after 6 weeks of training, the venous compliance increased significantly from pre to post training (0.0518 to 0.0619). The researcher proposed that low intensity walking with BFR could result in the improvement of limb venous compliance over the short periods (Iida et al. 2011).

In 2014, Fahs et al. investigated the effect of 6 weeks low intensity training with knee extension exercise on calf venous compliance. The subjects included 11 middle-age men and 5 women, age 40-64 years. The intervention consisted of training with unilateral knee extension exercise performed to volitional failure at 30%1RM, 3 times per week. One limb was occluded with the restriction cuff and the other was free flow condition. Both legs did the same exercise pattern with tempo of 1.5 seconds for both concentric and eccentric contraction for two sets for each limb. The results showed that after 6 weeks of training, free flow group did approximately 36% more total volume than BFR group. The average total training volumes of BFR and free flow group were 8,429kg and 13,171kg, respectively. Despite differences in volume, the calf venous compliance of both groups did no change significantly from pre to post intervention (BFR 0.0391 to 0.0371, free flow 0.0362 to 0.0362). The finding was contrary to Iida's study (2011) that 6 weeks of walking with BFR increased the venous compliance in older subjects. The reason might be the different in training protocol and duration of applied time. While Iida's study experimented the walking, Fahs' study used RT with machine. Besides, the duration of applied BFR in Iida's (2011) study was 20 minutes per session for 5 days per week (total 100 minutes per week), when Fahs' study (2014) was reported the training session lasting only 3.5-7.5 minutes (around 7-15 minutes per week). It was possible that the duration of BFR was too short or insufficient to induce positive changes in Fahs' study.

From the lines of mentioned evidence, the available data suggests that unlike high intensity training, low intensity RT with blood flow restriction in healthy subjects regardless of the age is likely to increase or (at least) maintain of the vascular function when indirectly measuring via large and small arterial compliance/elasticity index, central arterial compliance, or venous compliance.

Table 6. Effect of blood flow restriction resistance training on arterial compliance and stiffness

Study	**Duration**	**Subject**	**Intensity**	**Training intervention**	**Exercise**	**Primary outcome**
Kim et al. 2009	3 weeks	30 Healthy men	20%1RM 80%1RM	Low intensity BFR RT High Intensity RT	Leg press Knee extension Knee flexion	Large arterial compliance index increased 17.9% in BFR Low intensity BFR RT, 1.4% in High intensity Small arterial compliance index increased 1.4 % in BFR Low intensity BFR RT, decreased 6.4% in High intensity
Miyachi et al. 2004	16 weeks	28 healthy men	80%1RM	High Intensity RT	Leg extension Seated chest press Leg curls Lateral row Squat Sit-ups	Central arterial compliance decreased 19% Arterial stiffness increased 21%
Collier et al. 2008	4 weeks	30 pre-hypertensive men and women	65%1RM	High Intensity RT	Leg press Chest press Leg extension Lat pulldown Leg curls	Central arterial stiffness increased 14.5% Peripheral muscular arterial stiffness increased 8.7%

					Shoulder press Bicep curl and tricep press Abdominal crunch	
Tagawa et al. 2018	4 weeks	14 healthy men	75%1RM	High intensity RT	Biceps curl	The carotid arterial compliance decreased by 13%
Fahs et al. 2011	Acute effect	11 young healthy men	20%1RM 20%1RM 70%1RM	Low intensity BFR RT Low intensity RT High Intensity RT	Supine leg press Seated knee flexion Seated knee extension Seated plantar flexion	Both traditional high load and low load either with or without BFR resulted in similar acute post-exercise increases in large arterial compliance
Fahs et al. 2012	6 weeks	41 healthy young men	30%1RM 45%1RM 70%1RM	Low intensity BFR RT Moderate intensity RT High intensity RT	Knee extension Knee flexion	There was no significant difference from pre to post in large artery elasticity index and small artery elasticity index
Yasuda et al. 2014	12 weeks	21 healthy elder men and women	20-30%1RM	Low intensity BFR RT	Leg press Knee extension	The arterial stiffness was maintained
Ozaki et al. 2013	6 weeks	19 young healthy men	30%1RM 75%1RM	Low intensity BFR RT High intensity RT	Flat bench press	The carotid arterial compliance was significantly decreased (27%) in high intensity RT and slightly increased (13%) in low intensity BFR RT
Yan et al. 2018	8 weeks	24 healthy men	30%1RM	Low intensity BFR RT	Elbow flexion	There is the significant increase in aortic arterial compliance
Fahs et al. 2014	6 weeks	11 middle-age men and 5 women	30%1RM 30%1RM	Low intensity BFR RT Low intensity	Unilateral knee extension	The calf venous compliance of both groups did not change significantly from pre to post intervention

6.3.2 Ankle brachial index

The second method to indirectly measure vascular function is through ankle brachial index (Horiuchi & Okita 2012). The ankle brachial index or ankle brachial blood pressure index (ABI) is value of test that compares the systolic blood pressure of the lower and upper limbs (ankle and arm). Generally, ABI has been shown to be a specific and sensitive metric for the clinical diagnosis. The value of ABI is used in clinical practice as an indicator of peripheral arterial disease such as the risk of atherosclerosis in lower limb (Casey et al. 2019). The meta-analysis of 4 studies comprising 922 limbs demonstrated that the test of ABI score of less than or equal to 0.90 could be a non-invasive method to identify the serious peripheral arterial disease (Xu et al. 2013). Besides, the study also revealed that a low ABI value (less than 0.9) was associated with the severity and high extent of coronary arterial disease (Papa et al. 2013). Therefore, ABI is a good indicator for screening the risk of occurrence of many vascular dysfunctions.

Some studies using blood flow restriction technique also evaluated the effect of RT on ankle brachial index in subjects. For example, Yasuda et al. (2014) evaluated the cardiovascular effect of BFR RT at 20-30%1RM in older men and women. They performed 2 exercises twice a week for 12 weeks. Each session consisted of 1 sets of 30 repetition and 3 sets of 15 repetitions, with 30 second rest between set. The total occlusion time was average 11 minutes. After 12 weeks of training, no significant change in the ABI value was observed (from 1.13 unit to 1.15 unit) in blood flow restriction group. In the next study, Yasuda et al. (2015) changed the protocol to using elastic band instead of machine in older men and women upper limbs. They used the green band (heavy) and yellow band (light) for training 2 days per week for 12 weeks. Exercises were performed in controlled manner, 1.2 second concentric and 1.2 second eccentric contraction. The total occlusion time was average 9.5 minutes. The results were in accordance with the previous study that there was no significant change from pre to post observed in hemodynamic parameters including ABI value (from 1.17 unit to 1.14 unit) in group training with elastic band with BFR. Besides the muscle size of elbow flexors and extensors significantly increased (17.6% and 17.4% respectively). Then again, Yasuda et al. (2016) examined the effect of elastic band training with BFR in tight muscle size and vascular function in older women. The protocols separated the training group into low intensity with BFR and moderate to high intensity. Both groups performed squat and knee extension exercises, twice per week for 12 weeks. The intensity in this study was measured based on the type on elastic band. In squat and knee exercises, the moderate to high intensity group use 2 gold bands and 1 gold band, respectively. In the low intensity with BFR group, they use only 1 gold band for squat and one back band for leg extension, with black band twice lighter than gold band. The results showed that quadriceps muscle cross sectional area significantly increase (6.9% $p < 0.001$). Interestingly, the group moderate to high intensity did not significantly increase muscle size (1.5%, $p = 0.871$) although the band was twice the resistance level. However, both low intensity with BFR and moderate to high intensity groups did not report that significant changes in ABI pre and post 12 week of training (1.14 to 1.15 and 1.11 to 1.11, respectively). The estimate occlusion time in this study was approximately 10-11 minutes.

Few studies investigated the effects of BFR RT on ABI in healthy young adults, 18-30 years old. For example, Clark et al. (2011) reported no significant change in ABI after 4 weeks of knee extension exercise, comparing the group using low intensity with BFR (30%1RM) and high intensity (80%1RM). The ABI values reported in both groups from before and after training were 1.15 to 1.09 and 1.08 to 1.07, respectively. In agreement with Clark's study, Laswati et al. (2015) compared the different training intensity on the cardiovascular function and the matter of strength gains. The participants were 18 healthy men, age range from 26-45 years; they were randomly assigned into 3 groups, high intensity, low intensity, and low intensity with BFR. The intensity ranged from 70%1RM, 30%1RM, and 30%1RM with BFR, respectively. The exercise selection was biceps curl, twice per week for 5 weeks. The results demonstrated that strength gains measured via peak torque of isokinetic muscle contraction were significantly increased in only group high intensity (p = 0.003) and low intensity with BFR (p = 0.001) after 5 weeks of training. However, regardless of the intensity and BFR, the ABI values did not significantly change in all groups (1.11, 1.13, and 1.11, respectively).

From all above reviewed study, evidence can be appealing to conclude that in healthy young and older subject, regardless of the gender, are safe to train with low intensity with BFR protocol either by using machines or elastic band or free weight and either in upper and lower limb muscles. When considering the ABI value the collected data suggests that training at a spectrum of intensity does not significantly negatively affect the ABI value in chronic state, especially for 4-16 weeks of training with occlusion time around 10 minutes per session.

Table 7. Effect of blood flow restriction resistance training on ankle-brachial index

Study	Duration	Subject	Intensity	Training intervention	Exercise	Primary outcome
Yasuda et al. 2014	12 weeks	21 healthy elder men and women	20-30%1RM	Low intensity BFR RT	Leg press Knee extension	ABI value was observed from pre intervention 1.13 unit to post intervention 1.15 unit
Yasuda et al. 2015	12 weeks	17 healthy elder women	Elastic bands	Low intensity BFR RT	Arm Curl Triceps Pressdown	There was no significant change from pre to post observed in ABI value from 1.17 unit to 1.14 unit
Yasuda et al. 2015	12 weeks	14 healthy elder women	Elastic bands	Low intensity BFR RT	Arm curl Triceps Pressdown	There was no significant change from pre to post to 12 weeks of detraining observed in ABI value from 1.14 unit to 1.12 unit

						to 1.11 unit, respectively.
Yasuda et al. 2016	12 weeks	30 healthy elder women	Elastic bands	Low intensity BFR RT Middle to high BFR RT	Bilateral squat Knee extension	No significant changes in ABI pre and post intervention in both group (1.14 to 1.15 and 1.11 to 1.11, rspectively)
Clark et al. 2011	4 weeks	16 young healthy men and women	30%1RM 80%1RM	Low intensity BFR RT High intensity RT	Knee extension	The ABI values in both groups from before and after training were 1.15 to 1.09 and 1.08 to 1.07, respectively

6.3.3 Pulse wave velocity

Pulse wave velocity (PWV) is another indirect measurement of arterial stiffness (Horiuchi & Okita 2012). In research setting, PWV is widely used as a tool to diagnose the risk of cardiovascular disease in many studies (Kim & Kim 2019). In previous studies, there showed the associations between PWV with cardiovascular diseases such as coronary artery atherosclerosis (e.g Lee et al. 2015; Torii et al. 2015; Kim et al. 2018), cerebral artery atherosclerosis (e.g. Kim et al. 2010; Kim et al. 2016; Zhai et al. 2018), and carotid artery atherosclerosis (e.g. Munakata et al. 2005; Kubozono et al. 2015; Yang et al. 2018). There are several ways to measure PWV; however, some most widely used values of PWV in research setting include brachial-ankle PWV (baPWV), carotid-femoral PWV (cfPWV), and femoral -posterior tibial of ankle PWV (fptPWV). When interpreting the result, the PWV increases in value as the pulse wave travels faster in stiffened artery (Kim & Kim 2019). Therefore, the arterial stiffness and PWV are proportional. The higher the PWV value, the more arterial stiffness is.

In 2012, Vlachopoulos et al. did the first meta-analysis of 8169 participants and suggested that every 1 m/s increase of baPWV associated with the increased risk for total cardiovascular event by 12%, cardiovascular mortality by 13% and all-cause mortality by 6%. In the same way, Ben-Shlomo et al. (2014) reported that just 1 m/s increase in aortic PWV related to 7% increase in cardiovascular disease. Later on, the American Heart Association (2017) further reported that from the analysis till then of in 8 studies, 14700 subjects, the results showed that every 3.91m/s increase in baPWV was associated with 1.21 fold increase in cardiovascular risk. In addition, the baPWV cutoff value for predicting the risk of the cardiovascular disease was suggested at 15.43 m/s (Ohkuma et al. 2017). However, the cutoff values of PWV are various dependent on the studies. For example, Kim and Kim (2019) recently summarized that according to the current guideline of European Society of Cardiology (ESC) and European Society of Hypertension (ESH) in 2018, the cfPWV value of more than 10 m/s and baPWV value of more than 18 m/s, higher in than that of the American Heart Association, are indicative of risk of cardiovascular disease.

When considering PWV and BFR RT, studies are still sparse. The aforementioned study by Clark's (2011), showed that after 4 weeks of low intensity with BFR (3 times per week), the PWV value did not change significantly from pre to post intervention in healthy young subject, age 18-30 years. The PWV in this study was calculated from PWV between the femoral artery and posterior tibial artery of the ankle (fptPWV). The fptPWV value before and after intervention was slightly decreased but not reaching statistically significant (from 9.25 m/s to 8.73 m/s). The occlusion time in this study was reported 10-15 minutes per session (Clark et al. 2011). In 2013, Shimizu et al. conducted the study with 38 healthy older subjects, average age 71 years. The training protocol consisted of 4 exercises: leg extension, leg press, rowing and chest press. Every subject performed 3 sets of 20 repetitions per day, 3 times per week for total 4 weeks of intervention. The PWV was measured via the brachial-ankle pulse wave velocity (baPWV). The finding showed that the baPWV significantly decreased from 12.2 m/s to 11.4 m/s ($p < 0.05$). From the finding, it was appealing to say that BFR RT was potential in reducing arterial stiffness and enhancing vascular endothelial functions.

In contrast to Clark's study, Fahs et al. (2014) found that after 6 weeks of low intensity 30%1RM RT in lower restricted limb, the results showed that the PWV significantly increased from 8.9 m/s to 9.5 m/s (p = 0.036) from pre to post intervention. The PWV was measured from the distance from the femoral artery pulse to the posterior tibial artery pulse (fptPWV) as same as Clark's study. However, the researcher claimed the increase in PWV in this study was relatively small in magnitude (6.7%) (Fahs et al. 2014). The difference in results might be because the difference in subject age. While Clark's study investigated in young subject, Fahs' study was conducted with the study with middle age subject, age 40-64 years. Besides, although the intensity of training was considered low in Fahs' study (30%1RM), the exercise was performed until failure and there was the progressive increase in exercise volume in every week. Therefore, the training intensity might be considered high for subjects at this target age.

Recently, Credeur et al. (2019) examined the acute effect of hand grip resistance exercise with BFR on central cardiovascular hemodynamic response and aortic PWV. The subjects in the study included 15 men, average age 25 years. The exercise included hand grip exercise at 40%MVC with BFR, 60%MVC with BFR and 60%MVC without BFR. The contraction was fixed for 20 contractions per minute (1 second squeeze, 2 second relax). The findings showed that no significant change was observed in any central hemodynamic parameter between baseline and post exercise ($p > 0.05$) and aortic PWV only significantly increased from baseline and after training ($p = 0.02$) in the only condition of 60%MVC with BFR (6.65 m/s to 7.11 m/s). No significant increase was observed in condition of 40%MVC with BFR and 60%MVC without BFR.

Due to the lack of enough scientific studies directly investigating the PWV by BFR RT, it is very difficult to make a solid conclusion solely by these few available data about the effect of BFR RT on PWV. However, the traditional RT shed some light on this matter.

In the latest systematic review, Garcia-Mateo et al. (2020) researched the literature conducted from 1999 to April 2019 about the effect of RT on arterial stiffness by mean of PWV. From 16 included studies with various intensity and protocols, the analysis showed that in term of training intensity, long term training at low (<50%1RM) to moderate (50-69% 1RM) intensity RT did not result in the increase in arterial stiffness, especially in chronic state (Garcia-Mateo et al. 2020). The researchers concluded that from the evidence, practicing the RT of 2 days per week at least 4 weeks did not impair the cardiovascular health in term of increasing arterial stiffness (Garcia-Mateo et al. 2020).

A study by Au et al. (2017) investigated the effect of 12 weeks RT at various intensity ranges on arterial stiffness. The participants included 46 healthy young men, average age 23 years. The participants were randomly assigned to HR group performing 3 sets of 20-25 repetition at 30-50%1RM, LR group performing 3 sets of 8-12 repetitions at 75-90%1RM, or CN control group. The resistance exercise was designed to be full-body program and performed 4 times per week. The cfPWV was measured before and after intervention. After 12 weeks of training, the cfPWV significantly reduced in both groups to a similar degree ($p < 0.05$). The cfPWV value in HR group was decreased from 6.4 m/s to 5.7 m/s and the cfPWV value in LR group was decreased from 6.2 m/s to 5.8 m/s. In older study, Casey et al. (2007) examined the progressive RT for 12 weeks on arterial stiffness. The subjects included 48 healthy men, age 21-22 years, divided to training group and control group. The training group performed 2 sets of 8-12 repetitions to failure for 3 days per week. The exercises included 7 machines: leg extension, leg curl, leg press, lat pulldown, chest press, overhead press, and bicep curl. The results showed that there was no significant change from pre to post observed in the PWV from three measured sites in training group: carotid-radial, carotid-femoral, and femoral-dorsalis pedis (8.4 vs. 8.0 m/sec ($p = 0.06$); 6.5 vs. 6.3 m/sec ($p = 0.47$); 9.5 vs. 9.5 m/sec ($p = 0.83$), respectively).

From the current evidence both with BFR RT and with traditional RT, it shows that PWV is not significantly affected that much from practice of resistance exercise. The values might be slightly decreased or increased; however, the magnitude is small. Further research is needed to particularly draw a definite conclusion on the effect of BFR RT on PWV

Table 8. Effect of blood flow restriction resistance training on pulse-wave velocity

Study	Duration	Subject	Intensity	Training intervention	Exercise	Primary outcome
Clark et al. 2011	4 weeks	16 young healthy men and women	30%1RM	Low intensity BFR RT	Knee extension	The fptPWV was slightly decreased but not reaching statistically significant from pre to post (9.25 m/s to 8.73 m/s)
Shimizu et al. 2016	4 weels	38 healthy older men and women	20%1RM	Low intensity BFR RT	Leg extension Leg press Rowing Chest press	The baPWV significantly decreased from 12.2 m/s to 11.4 m/s post intervention ($p < 0.05$)
Fahs et al.2014	6 weeks	16 older men and women	30%1RM	Low intensity BFR RT	Unilateral knee extension	The fptPWV significantly increased from 8.9 m/s to 9.5 m/s ($p = 0.036$) from pre to post intervention
Credeur et al. 2019	Acute	15 healthy young men	40%MVC with BFR 60%MVC with BFR 60%MVC	Low intensity BFR training Moderate intensity BFR training Moderate intensity training	Handgrip training	The aortic PWV significantly increased from baseline after 60%MVC with BFR (6.65 m/s to 7.11 m/s)($p = 0.02$). No significant increase was observed in condition of 40%MVC with BFR and 60%MVC without BFR.
Au et al. 2017	12 weeks	46 healthy	30-50%1RM	Low to moderate intensity RT	Fullbody program	The cfPWV significantly reduced in both

		young men	70-90%1RM	High intensity RT		training groups to a similar degree ($p < 0.05$), from 6.4 m/s to 5.7 m/s in low to moderate intensity RT group and from from 6.2 m/s to 5.8 m/s in high intensity RT group.
Casey et al. 2007	12 weeks	48 healthy young men	70-80%1RM	Moderate to high intensity RT	Leg extension Leg curl Leg press Lat pulldown Chest press Overhead press Bicep curl.	No significant change from pre to post in carotid-radial PWV, carotid-femoral PWV, and femoral-dorsalis pedis PWV (8.4 vs 8.0 m/sec ($p = 0.06$); 6.5 vs 6.3 m/sec ($p = 0.47$); 9.5 vs 9.5 m/sec ($p = 0.83$), respectively))
Amonrim et al. 2021	Acute	3 older men and 14 older women	20%1RM 60%1RM	Low intensity RT Moderate intensity RT	Leg extension Leg press	Pulse wave velocity slightly increased in both group from 11.6m/s to 12.7m/s and 10.6m/s to 11.2ms in moderate intensity RT and low intensity RT, respectively

6.3.4 Flow mediated dilation

The last indirect method when investigating the vascular function is measuring the flow mediated dilation (Horiuchi & Okita 2012). The flow mediated dilation (FMD) is the noninvasive measurement based on ultrasound to detect the flow-mediated changes in arterial diameter (Raitakari & Celermajer 2000).

The meta-analysis by Inaba et al. (2010) reported that from 14 studies, 5,547 participants included, just 1% decrease in FMD was associated with 8% increase in the future risk of cardiovascular event. The research demonstrated that the cause of the increase in diameter of the measured artery came from the increase in shear stress (Tremblay & Pyke 2018) and increase in nitric oxide release (Green 2013), particularly from exercise. Besides, RT with blood flow restriction technique had showed to increase the shear stress and nitric oxide after training as the result of training induced reactive hyperemia (Horiuchi & Okita 2012). The reactive hyperemia refers to the state at which the magnitude of blood flows into the target muscle after a short period of blood flow restriction (Rosenberry & Nelson 2020). For instance, Mouser et al. (2017) investigated the acute effect of blood flow after low intensity with and without BFR RT in 137 participants, 64 men and 73 women. The training protocol included 1 set of 30 repetitions following by 3 sets of 15 repetitions with biceps curls exercise at 30%1RM. The blood flow was measured at baseline, during set 1, 2, 3, 4, and 1 and 5 minutes post exercise. The results showed that the degree of blood flow in BFR group significantly decreased when the cuff was inflated in both men and women (from 107 to 49.9 and from 65.5 to 22.6, respectively). The blood flow in group without BFR was 93.9 and 53.1 in men and women, respectively at baseline. During the RT set 1-4, both groups showed the significant increases in blood flow to working muscle both in men and women ($p < 0.001$); however, the magnitude of increase in BFR group was significantly less than without BFR group in all sets. Interestingly, at 1 minute after releasing the cuff, the blood flow significantly increased in BFR group (peak at 666.3 and 373.2 in men and women) compared to set 1-4 ($p < 0.05$), and not significantly different from a group without BFR (peak at 675.1 and 302.8 in men and women). The huge increase in the magnitude of blood flow change to muscle after the last set of training with BFR indicated the state of reactive hyperemia and because of this hyperflow state, it may in turn contribute to increase ability of artery to dilate.

Another example was done by Gundermann et al. (2012). They showed that low intensity with BFR performing leg extension at 20%1RM for 4 sets results in significant increase ($p < 0.05$) in femoral artery blood flow after finishing training. Besides, the increased flow remained significantly high ($p < 0.05$) until 15 minutes post-exercise. It is also purposed that another cause of increase flow mediated changes is due to BFR training induces the accumulation of metabolites and nitric oxide production (Wilson & Wilson 2009; Pearson & Hussain 2014) which act as the vasodilator stimuli.

In the last decade, only few studies had investigated the effect of BFR RT on FMD. For example, Credeur et al. (2010) studied the effect of 4 weeks hand grip training with BFR and investigated the effect on brachial artery FMD. The participants in this study included 12 healthy adults, average age 22 years. The training session consisted of hand gripping dynamometer for 20 minutes per day (15 repetitions per minute at 60% maximum voluntary contraction) for 3 days per week with the BFR cuff applying at the upper arm. The results showed that although the hand grip strength and forearm circumference significantly increased by 16.71% and 2.42% respectively ($p = 0.05$) in the BFR condition, the assessment in vascular function demonstrated the significant decrease in FMD by 30.36% ($p = 0.0001$) (pre-training = 0.27mm, post-training = 0.19mm). It was interesting to see that the shear stimulus area under curve was significantly higher after 4 weeks of training (5472.9 to 6776.2, $p < 0.05$) but there appeared the declination in FMD.

In 2013, Hunt et al. investigated the effect of unilateral dynamic plantar flexion exercise performed 3 sets at 30%1RM until volitional failure in 11 healthy men, average age 22 years. The BFR cuff was applied to the distal tight. The results showed that after 6 weeks of training, 3 sessions per week, the popliteal artery FMD significantly increased at post-2 weeks and post-4 weeks of training ($p = 0.002$ and $p = 0.014$, respectively) and returned to near baseline at end of week 6. The FMD at baseline was 5.0%, 7.6% at week 2, 6.6% at week 4, and 5.7% at week 6. Besides, the peak reactive hyperemia significantly increased during the intervention period ($p = 0.03$). Hunt et al. (2013) also reported the significant increase in maximal popliteal diameter after 6 weeks of training (from 6.06mm to 6.26mm, $p = 0.048$). It was well accepted that the shear stress was the main stimulus for increasing FMD. This study showed that the peak reactive hyperemia blood flow rose up to 1,716 and 1,736 ml/min while the normal blood flow at resting was only 256 and 254 ml/min in week 2 and 4, respectively, which corresponded to the significant increase in FMD in week 2 and 4.

Next study was conducted by Severin (2016) on the effect of isometric hand grip training. The participants in this were assigned to group BFR younger adult (n=8, age 22.2 years) and BFR older adult (n=10, age 63.2 years. Every participant had the healthy status prior to the study. The group younger and older adults BFR trained at 20% maximum voluntary contraction. The findings demonstrated that after 4 weeks of training, FMD increased to the higher degree in both younger and older adults (12.45% to 12.67% and 8.59% to 9.42%, respectively). Besides, the change in brachial artery diameter was also observed. In younger group at pre training, the resting and hyperemia diameter was 0.32mm and 0.34mm, respectively. In older group at pre training, the resting and hyperemia diameter was 0.36mm and 0.37mm, respectively. After 4 weeks of training, the resting and hyperemia diameter was 0.34mm and 0.36mm in younger group and 0.39mm and 0.43mm in older group, respectively. The finding of this study was contrast with Credeur's study (2010) who found the decrease in brachial artery FMD after hand grip training. The difference might be due to the difference in intervention intensities (20% vs 60% maximum voluntary contraction).

Concerning intensity and volume of training, Morishima et al. (2018) found that endothelial function (FMD) could be impaired when RT was done at high volume regardless of the low intensity, but maintained when volume was low even at high intensity. A cross-over study compared 3 RT protocols in 13 young healthy participants, average age of 21years. All participants visited the laboratory for 3 times separated by 7 days. The selected exercise was leg extension. In moderate-intensity exercise with moderate repetitions, participant performed 5 sets of 10 repetitions at 70%1RM, average 80.5kg. In low-intensity exercise with high repetitions, participant performed 40 repetitions for 5 sets at 30%1RM, average 34.1kg. And in high-intensity exercise with low repetitions, 3 repetitions for 5 sets at 85%1RM, average 96.5kg were performed. Brachial artery FMD was measured at 10, 30, and 60 minute post exercise. The results showed that at brachial artery FMD significantly decreased after exercising in high volume protocols: moderate and low intensities. The baseline FMD of moderate intensity trial was at 7.9% and at 4.2%, 4.4% and 3.5% at 10, 30 and 60 minute post exercise, respectively. The baseline FMD of low intensity trial was at 8.2 % and at 4.4%, 4.4% and 5.1% at 10, 30 and 60 minute post exercise, respectively. However, in the trial performing low volume, but high intensity, the FMD was maintained unchanged, 7.6% at baseline and 7.6%, 8.4% and 8.4% at 10, 30 and 60 minute post exercise, respectively (Morishima et al. 2018). These findings suggested that by reducing the duration of hypertension from RT by reducing the number of repetitions, this could be the training strategy to counteract the detrimental effects of high intensity resistance exercise on FMD.

Later on, Kambic et al. (2019) investigated the potential of BFR RT to improve vascular flow mediated dilation. The researcher recruited 24 patients with coronary artery disease into the study. During experiment, 12 patients were randomly assigned into program 8 weeks of BFR RT at intensity 30-40%1RM with leg extension exercise. The results showed that after 8 weeks of training, muscle strength significantly increased via 1RM measurement from 45.75kg to 54.71kg (p < 0.001) and SBP significantly decreased by 6.77mmHg ($p = 0.030$). However, there was a trend to slightly but not significantly improve brachial artery FMD in patient training with BFR RT from pre to post measurement (6.48% to 8.04%).

Recently, Early et al. (2020) recently examined the effect of blood flow restriction training on vascular function via measurement of FMD at brachial artery. The participant included 31 healthy adults, average age 23 years. The participants were randomly assigned to one of three groups: traditional RT (RES) 60%1RM, RT with BFR

(BFR) 30%1RM, and control group. The training protocols included arm extension, arm curl, leg extension, leg curl, and heel raise exercises performing exercises 2-3 times per week. The BFR group applied the cuff at both upper arms and upper thighs. The BFR performed total 3 sets of 30 repetitions each set and the RES performed 3 sets of 10 repetitions, for each session. The results found that the FMD did not change in control group but increased in both RES and BFR (9.9% and 8.1%, respectively) after 8 weeks of training.

The most recent cross-over study by Tsuchiya et al. (2022) compared the effect of slow-speed low intensity and normal speed high intensity RT in 11 young healthy men. The participants performed leg extension exercise at 80%1RM for 3 sets of 8 repetitions or 50% for 3 sets of 8 repetitions in slow or normal repetition velocities. The brachial artery FMD was evaluated at pre and post at 10, 30, and 60 minutes. The results showed that high intensity 80%1RM caused significant impairment of the brachial artery FMD at 30 (3.7 ± 2.7%) and 60 (3.7 ± 2.8%) min post exercise ($p < .05$). However, low intensity 50%1RM found no significant difference from baseline (Tsuchiya et al. 2022). Therefore, it is possible that low or moderate intensity RT, rather than high intensity (>60%), benefits or at least maintains the endothelial flow mediated dilation function.

From the current evidence, there shows the trend that the low to moderate intensity RT with BFR technique may potentially improve, or at least maintain, FMD, especially in dynamic contraction. Five of seven studies showed the increase in FMD to the certain degree. All four studies using BFR dynamic exercises demonstrated the increase in FMD of brachial artery and popliteal artery. Still, exercise intensity and volume may play the significant role in both isometric and dynamic contraction on FMD. From the available data, it seems that BFR RT is a safe alternative program when considering the flow mediated dilation in dynamic exercise. However, further research is warranted to confirm the relationship between BFR RT and FMD.

Table 9. Effect of blood flow restriction resistance training on flow-mediated dilation

Study	Duration	Subject	Intensity	Training intervention	Exercise	Primary outcome
Credeur et al. 2010	4 weeks	12 healthy young men and women	60%MVC	Moderate intensity BFR training	Handgrip training	FMD significantly decreased by 30.36% (from 0.27mm to 0.19mm)(p = 0.0001).
Hunt et al. 2013	6 weeks	11 healthy young men	30%1RM	Low intensity BFR RT	Dynamic plantar flexion	Maximal popliteal diameter significantly increased after 6 weeks of training (from 6.06mm to 6.26mm, p = 0.048)
Severin et al. 2016	4 weeks	8 healthy young and 10 healthy older adults	20%MVC	Low intensity BFR training	Handgrip training	FMD increased in both younger and older adults (from 12.45% to 12.67% and from 8.59% to 9.42%, respectively)
Morishima et al. 2018	Acute	13 healthy young men	30%1RM 70%1RM 85%1RM	Low intensity RT Moderate intensity RT High intensity RT	Leg extension	Brachial artery FMD significantly decreased after exercising in high volume moderate and low intensities protocols Brachial artery FMD was maintained unchanged in low volume high intensity protocol
Kambic et al. 2019	8 weeks	24 patients with coronary artery disease	30-40%1RM	Low intensity BFR RT	Leg extension	Brachial artery FMD in patient slightly increased from pre to post measurement (from 6.48% to 8.04%)
Early et al. 2020	8 weeks	31 healthy young women	30%1RM 60%1RM	Low intensity BFR RT Moderate intensity RT	Arm extension Arm curl Leg extension Leg curl Heel raise	Brachial artery FMD increased in both training groups (8.1% and 9.9%, respectively).

In summary, it has been fairly well-documented that low intensity BFR RT can produce the very satisfying results when considering how low the intensity is. It can be the alternative to high intensity RT either for young or older participants because it can reduce the external load used when training, reducing joint stress, inducing metabolic stress. However, the side effect on vascular functions should always be one of the main concerns of BFR. From the available evidence, it seemed that the effect of BFR RT on arterial compliance and stiffness, ankle-brachial index, pulse-wave velocity, and flow mediated dilation would be beneficial or at least maintained. Factors such as intensity and volume were the main variables to be concerned when programmed. With low volume (e.g. number of repetitions) and low to moderate intensity (e.g. 30-50%1RM), BFR RT should be recognized as a safe training alternative for most practitioners regardless of the age and not be detrimental to vascular functions. However, whether the combination of high and low intensity RT with BFR produces similar or better improvement in vascular function is yet to be determine. Therefore, this study wanted to fulfill this gap of knowledge, investigating the effects of combining program compared to traditional high intensity RT.

7. OMNI-RES

The Rating of Perceived Exertion (RPE) is a self-assessment tool that individuals use to rate the intensity of their exercise based on how hard they feel their body is working. This subjective measure is commonly applied to monitor the intensity of aerobic exercises, providing valuable feedback to ensure the exercise is performed within a safe intensity range as perceived by the individual. RPE reflects several physiological factors, such as heart rate and breathing rate, which correlate with the exertion level. The Borg RPE scales are widely used due to their simplicity and effectiveness in various exercise settings (Borg, 1988). Recently, ***the OMNI-RES scale has gained traction for its application in resistance training***, offering a tailored approach to assessing perceived exertion during such exercises.

The OMNI-RES scale, introduced by Robertson et al. (2003), was designed as an alternative to the traditional Borg RPE scales. This scale allows participants to self-assess their perceived level of muscular effort during resistance exercises. During its application, participants are asked to rate "***how hard they perceive their muscles to be working by selecting a number from the scale***", which ranges from 0 to 10. It ranges between "Extremely easy" to "Extremely hard." At the end of the resistance training session, individuals use the OMNI-RES scale to report their perceived exertion, with a score of 0 indicating a state of maximal rest, such as sitting, and a score of 10 representing an effort beyond what they could sustain during the session.

Numbers of previous studies have used OMNI-RES in their experiments. It was found that generally, OMNI-RES scores would increase in association with two training factors which were ***increased number of sets*** and ***increased exercise intensity***. For example, Colado et al. (2012) investigated the effect of shoulder exercise front raise and lateral raise in 20 males and females. They compared between low intensity set using elastic band that could be performed for 15 repetitions and high intensity set using elastic band that strength +50% of previous set. The results demonstrated that the OMNI-RES scores of high intensity set were 8.95 and 9.15 for front raise and lateral raise, respectively, while the OMNI-RES scores were just 6.0 and 6.15, respectively in low intensity set.

Similarly, da Silva et al. (2017) compared bench press exercise in elder females that performed 3 sets of 10 repetitions. The average load used for these elder females was 19.7kg. It was found that OMNI-RES score significantly increased from set 1 to set 3 from about 6 to 8.5, together with increase in heart rate from about 80bpm to 100 bpm, respectively.

Moreover, Farah et al. (2009) conducted a study employing sets of exercises including bench press, knee extension, row, knee curl and front raise. Each exercise was performed for 3 sets at 50%1RM. The number of repetitions were 12, 9, and 6 repetitions from set 1 – 3, respectively. The conditions were that first experiment was assigned with 30 second rest interval and second experiment was assigned with 90 second rest interval. It was clearly showed that OMNI-RES was higher with shorter rest compared to long rest. Results demonstrated that RPE in the first repetition at set 3 was 2.8, 3.2, 3.0, 3.3 and 2.9 for bench press, knee extension, row, knee curl and front raise, respectively for long rest. In contrast, OMNI-RES score for shorter rest was higher in the first repetition at set 3 (3.1, 4.1, 3.5, 3.9, and 3.5, respectively).

In the same way, Duncan et al. (2006) examined the relationship between OMNI-RPE and muscle activity during dynamic leg extension exercise. Twenty participants were asked to perform one set of leg extension exercise at 30%1RM, 60%1RM, and 90%1RM. Moreover, electromyography data were collected from the rectus femoris, vastus lateralis, and vastus medialis muscles during training as well. The findings demonstrated muscle activity, as electromyography increased, increased with exercise intensity in all muscle groups. Moreover, muscle activity was positively related to OMNI-RPE. Therefore, as intensity increased, muscle activities increased, and perception of effort increased accordingly.

Hollander et al. (2008) conducted an intriguing study that involved a range of exercises, including the lat pulldown, leg press, bench press, leg extension, military press, and leg curl. The study involved seven healthy young males who already had experience with resistance training. Each participant was required to complete four sets of each of the six exercises, resulting in a total of 24 sets per training session. The findings revealed a consistent, linear increase in OMNI-RES scores throughout the session, starting from a score of 1.5-2 during the first set of the lat pulldown and rising to a score of 8 by the final set of the leg curl. This progression highlights how perceived exertion tends to increase as a workout progresses, reflecting the cumulative fatigue experienced by the participants. Additionally, the study observed that as OMNI-RES scores increased, participants also reported higher levels of pain, indicating a correlation between perceived exertion and discomfort as the workout progressed.

Last but not least, the study by Robertson et al. (2005) found that rate of perceived exertion in active muscle would be higher that over perception scores in exercise like biceps curl and knee extension. The researchers recruited 25 females and 25 males to the study, assigning them to perform 3sets of 14, 10, 6 repetition, respectively, at 50%1RM. Then the OMNI-RES score of active muscle and overall body were observed. The results demonstrated that the highest OMNI-RES score for active muscle for biceps curl was 8.3 and for knee extension was 9.6 while OMNI-RES increased as the set continues. Moreover, OMNI-RES score did not differ between females and males at any measurement point within each set.

Table 10. Previous studies investigating OMNI-RES from resistance training

Study	**Exercise**	**Intensity**	**Type of RPE**	**Outcomes**
Colado et al. (2012)	Front raise Lateral raise	Low and high intensity 1 sets of 15 reps	OMNI-RES	RPE increased with exercise intensity
da Silva et al. (2017)	Bench press	3 sets x 10 reps 10RM	OMNI-RES	RPE increased with the number of sets
Farah et al. (2009)	Bench press Knee extension Row Knee curl Front raise	3 sets x 12, 9, 6 reps 50%1RM	OMNI-RES	RPE increased with short rest
Duncan et al. (2006)	Leg extension	1 set x 1 reps 30%1RM, 60%1RM, and 90%1RM	OMNI-RES	RPE increased with exercise intensity
Hollander et al. (2008)	Lat pulldown Leg press Bench press Leg extension Military press Leg curl	4 sets x 10 reps 65%1RM	OMNI-RES	RPE increased with the number of sets
Robertson et al. (2005)	Biceps curl Knee extension	3sets x 14, 10, 6 reps 50%1RM	OMNI-RES	RPE increased with the number of sets

In summary, the OMNI-RES scale is a highly effective tool for assessing perceived exertion during resistance training. It allows individuals to self-rate their level of effort, which tends to increase as the workout progresses, particularly with higher intensities, more sets, and shorter rest intervals. The scale has been shown to correlate well with physiological factors like muscle activity and heart rate, making it a valuable resource for both researchers and practitioners in monitoring and adjusting training intensity. Overall, the OMNI-RES scale provides an understanding of how perceived exertion evolves during resistance training, aiding in the safe and effective design of resistance training programs.

CHAPTER 3

METHODOLOGY

In this chapter, the information regarding the research design, study setting, participants, research instrument, research intervention, data collection procedure, data analysis, and validity and reliability were presented.

Study design

The aim of this study was to investigate and compare the morphological and physiological adaptations resulting from two different training programs: TRAD and LLpBFR. This study employed an experimental research design, incorporating two experimental groups to address the research questions. In order to control for potential confounding factors, the volume set, exercise order, execution pattern, repetition tempo, and rest interval time were standardized between groups. Only individuals with no prior structured resistance training experience were eligible to participate, to minimize the impact of experience-related biases on current performance. The resistance training was conducted in a laboratory setting, under the supervision of a certified personal trainer. Participants must sign a consent form, and underwent baseline testing prior to the intervention. Additionally, post-intervention testing was conducted one week following the final training session.

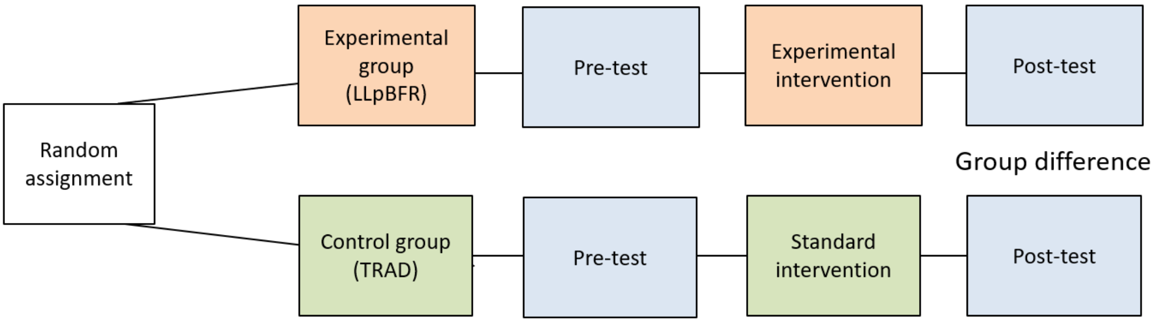


Figure 28. Experimental research design

Study setting

This study was conducted at controlled laboratory setting and gym room of Faculty of Sport Science, Burapha University, providing a controlled environment for investigating the morphological and physiological adaptations as result of different training programs. The training session was staffed by certified personal trainers and researchers to ensure safe and effective training protocols. The controlled environment of the laboratory and gym room eliminated the influence of extraneous variables, enabling researchers to isolate the effects of resistance training on the body.

Participants

The number of participants in this study was calculated by G*power version 3.1.9.4. Test family was F tests. The statistical test was MANOVA: Repeated measures, within-between interaction. The input parameter was Effect size = 0.75, α err prob = 0.05, Power(1- β err prob) = 0.80. As a result, the total sample size was 17. The input parameter was adapted from previous study which employed the similar experimental design (Zaroni et al. 2019). Considering 20% dropout rate allowed, therefore the total number of participants in this study was 20.

The participants of this study were divided into two training groups equally, TRAD (n=10) and LLpBFR (n=10), by web-based research randomizer. This web-based randomizer guaranteed that the participants were randomly assigned, thereby minimizing the potential for systematic bias and enhancing the validity of the study.

The inclusion criteria were adapted from previous study of Lacerda et al. (2020) as follows:

1. Young untrained men (age between 18 and 30 years old).
2. Has been identified as healthy, verified by general health check and blood lipid testing.
3. Has no sign of hypertension and normal ABI confirmed by certified clinician at Burapha University Hospital.

4. Has not participated in well-structured RT program during the last 6 months before this study.
5. Has not had functional limitations that will influence the 1RM test or the training protocols.
6. Has not had history using of pharmacological substances, ergogenic drug or steroids that will have effect of the change in muscle thickness or strength before the experiment.
7. Has completed the first-line Risk-stratification screening questionnaire recommended by Nascimento et al. (2022) (Appendix. B)
8. Has agreed to sign an informed consent form. (Appendix. F)

The exclusion criteria are as follows:

1. Participants who are unwilling to comply with the study protocol, such as following the prescribed resistance training program and attending all scheduled assessments.
2. Participants who are unable to carry out resistance training due to injury during the course of training.
3. Participants who have been detected any unstable medical conditions during the experimental time.
4. Participants who refuse to give informed consent.

Research instruments

The instruments used in this study are as follows: (Appendix A)

1. Preacher curl machine (Body-Solid, USA) for biceps curl exercises.
2. Knee extension machine (Body-Solid, USA) for knee extension exercises.
3. Isokinetic machine (ISOFORCE, Germany) for testing maximal isometric strength.

4. Clinical pneumatic blood flow restriction cuffs (H+CUFF, USA) which is officially listed by The United States Food and Drug Administration (FDA) as class 1 medical device.
5. Handheld vascular doppler ultrasound for verifying the arterial occlusion pressure (AOP).
6. Elastic wraps (GRIZZLY FITNESS, Canada) with 7.6cm. width and 160cm. length.
7. B-Mode Ultrasound Device (LOGIQ E10 Series, GE Healthcare, USA) for measuring the increase in muscle thickness of vastus lateralis and biceps brachii.
8. Magnetic resonance imaging (Vantage Elan, Canon, USA) for measuring the increase in muscle cross-sectional area of vastus lateralis and biceps brachii.

Research interventions

Familiarization

In the familiarization session, one week prior to 1st week of intervention, participants were introduced to the training equipment and explained about the basic anatomical movement in the exercises and history and usage of blood flow restriction.

Dynamic and isometric strength tests

The dynamic and isometric strength were tested at prior to intervention, at week 3 and the post intervention at week 7.

Each participant was tested for their dynamic strength by leg extension and biceps curl exercises. All strength testing procedures were following the guideline according to the testing recommendation of National Strength and Conditioning Association (Brown, 2017). Before testing, the specific warm-up included one specific warm-up set of the given exercise. The intensity was low enough to be performed for 5-10 repetitions easily. 1 minute rest was given at this point. Another one specific warm-up set was performed at the estimate resistance that allowed for 3-5 repetitions. 2 minute rest was given at this point. The last specific warm-up set was performed at the estimate resistance that allowed for 2-3 repetitions. At this point, 4 minutes rest was given before the strength test begins. The dynamic strength was referred as 1 repetition maximum (1RM) test. This test was conducted under the supervision of the researcher. 1RM was assessed by finding the greatest load each participant could lift for only one repetition, with proper form, through a full range of motion.

For leg extension exercise, the participants were instructed to sat securely on the leg extension machine (Body-Solid, USA), and move the load from a starting point (knee flexion approximately at 90 degree) to full knee extension (0 degree of knee flexion) one time per attempt. For biceps curl exercise, the participants sat securely with upright torso and placing elbow on supported pad of preacher curl machine (Body-Solid, USA). Afterwards, participants were instructed to lift the load from a starting point (elbow straight) to full elbow flexion (approximately 130 degree of elbow flexion) one repetition per attempt. In both exercise testing, the load was gradually increased following each successful attempt in order to increase the intensity for the next attempt. The process continued until the maximum load the participant could lift for 1 repetition was obtained. The recovery period of each attempt was 3-4 minutes. All mentioned testing procedures were carefully supervised.

Besides, the isometric strength test was assessed. The isokinetic machine (ISOFORCE, Germany) was utilized to assess the peak torque of knee extensors and elbow flexors. The isometric strength test of knee extensors was conducted by participant sitting with belt straps securely fixing the torso and being instructed to extend knee against immoveable knee pad at the joint angle of 60 degree of knee flexion (full knee extension = 0 degree knee flexion). Participants were asked to extend the knee as explosively as possible and holding for 3 seconds. 3 repetitions were allowed with 15 seconds rest between repetition. Similarly, the isometric strength test of elbow flexors was conducted by participant lying on machine bench with belt straps securely fixing the torso and being instructed to flexion elbow against immoveable grip at the joint angle of 90 degree of elbow flexion. Participants were asked to flex elbow as explosively as possible and holding for 3 seconds. 3 repetitions were allowed with 15 seconds rest between repetition. The highest value of peak torque from 3 attempts was used in analysis. The protocols for the numbers of repetition tested, holding time, and rest interval was followed previous work (Sarabon et al. 2021).

Practical blood flow restriction familiarization

During the familiarization session, participants was instructed on the appropriate pressure for applying elastic wraps (GRIZZLY FITNESS, Canada) during practical blood flow restriction exercises. The standardized protocol for this study was based on the suggestions outlined in the study by Bell et al. (2022).

Initially, participants were fitted with a clinical pressurized cuff (H+CUFF, USA) and exposed to the lowest pressure capable of completely occluding arterial blood flow. The applied pressure was increased gradually of 10-20 mmHg until reaching the arterial occlusion pressure (AOP). The validity of AOP was confirmed by using a portable vascular doppler. This technique was investigated in previous studies and showed to be highly valid (Zeng et al. 2019; Brekke et al. 2020, Lima-Soares et al. 2022). Next, participants was exposed to a pressure of 40% of their individual AOP, as previously described by Bell et al. (2021), on both their upper and lower extremities. The pressure was alternated on and off at a 12:22 second ratio for 5 cycles to allow participants to become acclimated to the perceived pressure.

Once participants became comfortable with the pressure, they were given the opportunity to use the elastic wraps (GRIZZLY FITNESS, Canada) to apply the same relative perceived pressure of 40%AOP. According to Bell et al. (2021), the error in application was very minimal, within the range of 1-5 mmHg above or below the target pressure. This method was expected to result in a more precise application of pressure compared to the perceived pressure scale, as demonstrated in the study by Wilson et al. (2013). The reason for choosing an arterial occlusion pressure of 40% was that this pressure was high enough to induce chronic morphological and physiological adaptations, as described in the exercise prescription model for BFR resistance training (Patterson et al. 2019), while still being minimal compared to the highest recommended pressure (80%AOP).

Risk assessment

All participants were evaluated for thrombosis risk factors by using the assessement questionnaire recommended by Nascimento et al. (2022). The questionnaire, consisting of 4 sections and 45 questions, assessed the participant's health and medical history to determine their potential risk of experiencing elevated blood pressure or abnormal cardiovascular responses during BFR training. The questions were scored on a scale of 1 to 5, with a higher score indicating a greater potential severity of symptoms. The total score were used to categorize the participant's risk level for deep vein thrombosis (DVT) into 4 categories: low risk (<10%) for a score of 0-1, moderate risk (10-20%) for a score of 2, high risk (20-40%) for a score of 3-4, and the highest risk (40-80% with 1-5% mortality) for a score greater than 5. To participate in this study, participants must have a total score of 1 or less (Appendix B).

Muscle thickness and area assessment

Ultrasound imaging

The muscle thickness of both the vastus lateralis and biceps brachii were evaluated prior to the initiation of the training program (at week 0) and after its completion (at week 7) by utilizing ultrasound imaging technique. The application of a transmission gel in the area where images was obtained was mandatory, and a B-mode ultrasound imaging device (LOGIQ E10 Series, GE Healthcare, USA) equipped with a linear probe was utilized in accordance with the protocols outlined in Franchi et al. (2018). The measurement of muscle thickness was determined as the linear distance between the deep and superficial aponeuroses of the muscle of interest, utilizing a frequency of 5-10MHz. For the vastus lateralis, the thickness was measured at three points along the femur; a proximal point at 30%, a middle point 50%, and a distal point 7 0% of the femur length, as identified from the greater trochanter to the lateral epicondyle of the femur. This measurement protocol was adopted and adapted from Lacerda et al. (2020).

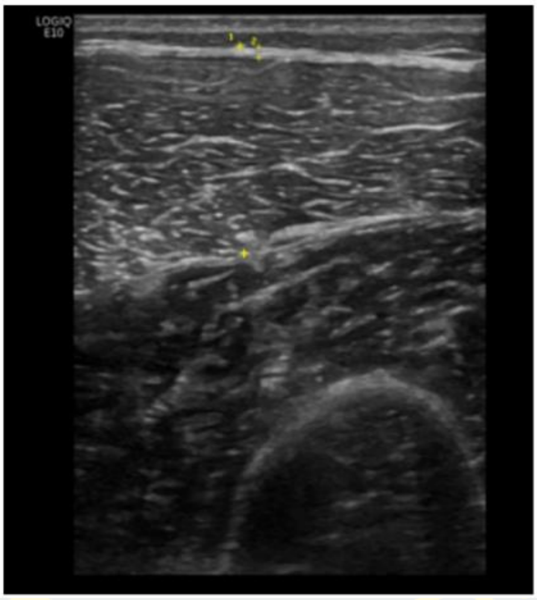


Figure 29. Example image of muscle thickness of vastus lateralis

Similarly, for the biceps brachii muscle, the thickness was measured at three points along the humerus; a proximal point at 50%, a middle point at 60%, and a distal point at 70% of the humerus length, as identified from the acromial process to the lateral epicondyle of the humerus. This measurement protocol was adopted and adapted from Matta et al. (2011). As muscle hypertrophy was reported as being non-uniform within the working muscles in RT literature (e.g. Mangine et al. 2018; Jessee et al. 2018; Hirono et al. 2020; Zabaleta-Korta et al. 2020), so the measurement of muscle thickness from various points would provide a comprehensive understanding of the muscle regional hypertrophy.

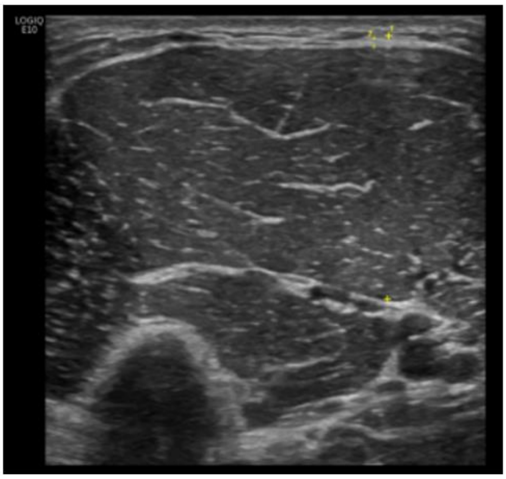


Figure 30. Example image of muscle thickness of biceps brachii

Furthermore, various architectural features of the vastus lateralis muscle, including fascicle angle, fascicle length, and fascia thickness, were measured using ultrasound imaging. Data were collected from the muscle at 30% of its length. The fascicle angle was determined as the angle between the fascicle and the deep aponeurosis. Fascicle length was measured as the length of the fascicular path spanning from the superficial to the deep aponeuroses, as observed on the ultrasound image. Additionally, fascia thickness at 30% region above muscle thickness was recorded to investigate the response of these structural elements to a resistance training program.

Figure 31. Example image of muscle architecture of vastus lateralis

Magnetic resonance imaging

The muscle cross-sectional area of both the vastus lateralis and biceps brachii were evaluated prior to the initiation of the training program (at week 0) and after its completion (at week 7) by utilizing magnetic resonance imaging technique. The measurement of muscle cross-sectional area via Magnetic resonance imaging (Vantage Elan, Canon, USA) was the gold-standard of practice. The muscles that were measured include vastus lateralis and biceps brachii. The measurement steps were conducted by 1.5-T scanner as the following: firstly, a standard axial T1-weighted sequence (TR/TE = 600/20 msec, thickness/gap = 7/0.5 mm, matrix = 256x 256, FOV = 32-36 cm), secondly, axial T2-weighted fat-saturated sequence (TR/TE = 4000/70 msec, thickness/gap = 7/0.5 mm, matrix = 256x 256, FOV = 32-36 cm), thirdly, coronal T1-weighted sequence (TR/TE = 600/20 msec, thickness/gap = 6/0.5 mm, matrix = 256x 256, FOV = 32-36 cm); and lastly coronal T2-weighted fat-saturated sequence (TR/TE = 4000/70 msec, thickness/gap = 6/0.5 mm, matrix = 256x 256, FOV = 32-36 cm). Measurement points between MRI and US were identical, which were at 50%, 60%, and 70% of biceps brachii and at 30%, 50%, and 70% for vastus lateralis.

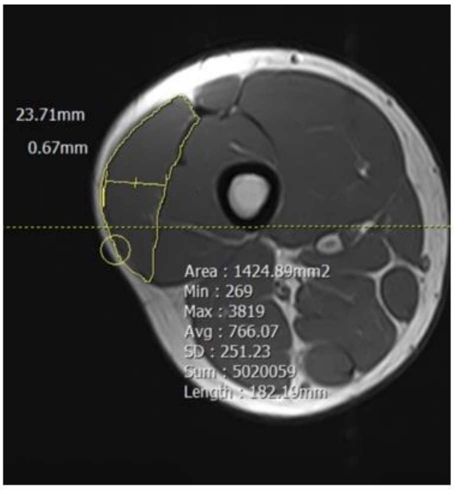


Figure 32. Example image of muscle cross-sectional area of vastus lateralis

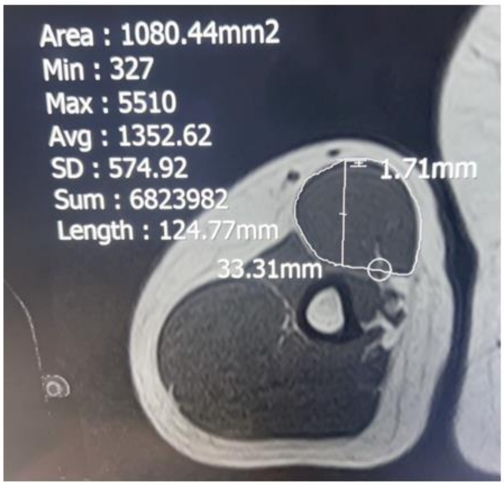


Figure 33. Example image of muscle cross-sectional area of biceps brachii

Chronic vascular function via ABI

The evaluation of the ankle-brachial index was performed on each participant prior to the commencement of the training program (at week 0) and post intervention (at week 7). The protocol was applied from guidelines set forth by the American Heart Association (Aboyans et al. 2012). Participants were instructed to rest in a supine position for a period of 5 minutes, with the aim of promoting relaxation. It was imperative that participants remain still during the measurement process. The systolic blood pressure of the upper arm was measured first, utilizing an automatic blood pressure device to measure systolic blood pressure of the right arm first and followed by the left arm. Then the same process was repeated for the systolic blood pressure measurement of the lower leg measuring at right and left ankle. The ABI calculation was performed as follows

ABI = Highest pressure of lower leg/the highest pressure of upper arm

Resistance training protocols

The resistance training sessions was conducted in the gym room of Faculty of Sport Science, Burapha University, under the close supervision of the researcher in the afternoon on every Monday. The knee extension machine and preacher curl machine (Body-Solid, USA) were the primary equipment utilized during the 6-week programs.

In the main training session, in the first and second weeks, participants were performing only 3 sets of both exercises to failure. This low volume was in accordance with the suggestions of the American College of Sports Medicine for beginners and to minimize exercise-induced muscle damage and delay onset muscle soreness. Subsequently, the volume sets were progressively increased, with the third and fourth weeks consisting of 6 sets of knee extension and preacher curl to failure. Finally, the volume sets increased to 8 sets of each exercise to failure in the fifth and sixth weeks, with the aim of maximizing muscle hypertrophy and avoiding adaptation plateaus (Schoenfeld et al. 2017). Each training session commenced with a 5-minute warm-up on a light and easy cycling machine, following by specific resistance warm-up of 15 repetitions of 5kg dumbbell thruster exercise for 3 sets with 1 minute rest between set. After finishing both warm-ups, 3 minutes rest was provided. The reason for selecting dumbbell thruster exercise to be specific resistance warm-up was because it involved both movements at elbow joint and knee joint which deem suitable for preparing the elbow flexors and knee extensors muscles for the main training exercises.

For the Traditional Resistance Training Protocol (TRAD), participants performed 3 to 8 sets of knee extension and preacher curl at a load of 70%1RM, striving for as many repetitions as possible until concentric muscular failure was reached. Concentric muscular failure was defined as the point at which repetition could no longer be completed through a full range of motion (Loenneke et al. 2011). A rest interval of 60 seconds was provided between set, in accordance with meta-analysis which found that longer rest between set (>60 seconds) could be beneficial for hypertrophy training as it allowed more repetitions to be performed, directly affecting training volume (Grgic et al. 2017). The phasic duration was performed at a slow to moderate velocity, with a 2-second concentric contraction, 2-second hold at peak contraction, and 2-second eccentric contraction (2-2-2s) in accordance with ACSM guidelines (Ratamess et al. 2009). The total duration per repetition was equal to 6 seconds, within the recommended range, 0.8 - 8 seconds, for muscle hypertrophy (Schoenfeld et al. 2015).

For Low Load with Practical Blood Flow Restriction Protocol (LLpBFR), participants performed 2 to 4 sets of knee extension and preacher curl at a high load of 70%1RM until concentric muscular failure. In the final 1 to 4 sets, the protocol shifted to low intensity with practical blood flow restriction, with participants performing as many repetitions as possible at a load of 30%1RM until concentric muscular failure. The repetition duration and rest interval remained similar between the two protocols.

The training intensity, expressed as a percentage of 1RM, was determined for each participant based on the dynamic 1RM strength test conducted in Week 0, and readjusted following the re-evaluation of the dynamic 1RM test at the end of Week 3. Besides, in every training set, participants were encouraged verbally to "trying to perform as many repetitions as possible and feeling the contraction and stretching of working muscle in every repetition". All training sessions were carefully supervised by certified personal trainer.

In order to control confounding factors from exercising, other resistance exercises were prohibited for both groups. Participants were informed to abstain from any other structured resistance training program during the duration of the experiment. Full resistance training program details were illustrated in Table 11.

Table 11. Resistance training programs

Exercise order: A>B **Tempo: 2-2-2 (CON-ECC-ISO)** **Number of repetitions: to failure** **Rest: 60 seconds** **Training time: Afternoon** **Frequency: 1 session/week** **Location: Fitness room, Faculty of Sport Science, Burapha University** **BFR technique: practical blood flow restriction (Elastic wraps)**	**WEEK 1-2**	**WEEK3-4**	**WEEK5-6**
	TRAD	**TRAD**	**TRAD**
	A: Knee extension 3sets 70%1RM **B: Preacher curl** 3sets 70%1RM	**A: Knee extension** 6sets 70%1RM **B: Preacher curl** 6sets 70%1RM	**A: Knee extension** 8sets 70%1RM **B: Preacher curl** 8sets 70%1RM
	Total set: 3 sets per muscle	**Total set: 6 sets per muscle**	**Total set: 8 sets per muscle**
	LLpBFR	**LLpBFR**	**LLpBFR**
	A: Knee extension 2sets 70%1RM 1sets 30%1RM+pBFR **B: Preacher curl** 2sets 70%1RM 1sets 30%1RM+pBFR	**A: Knee extension** 3sets 70%1RM 3sets 30%1RM+pBFR **B: Preacher curl** 3sets 70%1RM 3sets 30%1RM+pBFR	**A: Knee extension** 4sets 70%1RM 4sets 30%1RM+pBFR **B: Preacher curl** 4sets 70%1RM 4sets 30%1RM+pBFR
	Total set: 3 sets per muscle	**Total set: 6 sets per muscle**	**Total set: 8 sets per muscle**

OMNI-RES

The OMNI-resistance exercise scale (OMNI-RES) was introduced in the familiarization session. The OMNI-RES was developed based on the Borg's rate of perceived exertion scale (Borg, 1998) and it was represented in the numeric score ranging from 0 to 10 (Robertson et al. 2003). This scale would be completed after every training session. The OMNI-RES would represent "How hard do you feel your muscles are working?" based on the subjective perception of maximal effort. The number 0 represented "extremely easy", 2 for "easy", 4 for "somewhat easy", 6 for "somewhat hard", 8 for "hard", and 10 for "extremely hard". The validity coefficient of OMNI-RES was reported in previous study from 0.94 to 0.97 (Lagally & Robertson 2006)

Application of practical blood flow restriction

The implementation of the practical blood flow restriction technique was adhered to the guidelines and procedures outlined by Loenneke et al. (2009). In the context of this study, the utilization of elastic wraps, rather than traditional pressurized cuffs as described by Yamanaka et al. (2012), Lowery et al. (2014), and Behringer et al. (2017), was deemed to be the preferred method of application. Only the participants assigned to the LLpBFR group would have the elastic wraps (GRIZZLY FITNESS, Canada) applied to the proximal region of their quadriceps muscle near the inguinal crease, and to the insertion point of the deltoids muscle on the upper arms. The application of the wraps would commence at the beginning of the first working set; however, it should be noted that the wraps would not be tightened during the heavy training sets. The practical blood flow restriction wrap would only be tightened to a level of perceived pressure at 40%AOP of each individual, which the participants reported as similar to their familiarization session, prior to the commencement of the low intensity sets. The wraps would remain tightly fastened for the duration of these sets and would be removed immediately after all sets were finished. This study complied to the guideline for safety concerns, as stated by Patterson et al. (2019), that the total duration of arterial occlusion did not exceed 10 minutes.

Data Collection Procedure

Prior to the initiation of the experiment, participants underwent a familiarization phase during Week 0. This phase introduced them to exercises, including the Leg extension and Preacher curl machine (Body Solid, USA), as well as the practical blood flow restriction protocol, its principles, and applications. All participants underwent a risk assessment screening and signed a consent form before starting the training. Both groups had their biceps brachii and vastus lateralis muscle thickness, cross-sectional area, strength, and ABI measured at the Pre-test.

The pre-test measurements were conducted within two weeks before the first training session. Strength test including 1RM test of knee extension and preacher curl as well as isometric strength of knee extension and elbow flexion. Moreover, 1RM strength was re-assessed mid-intervention at the end of Week 3 to adjust training loads, ensuring intensity remained high to maximize adaptation.

Participants in both groups—TRAD and LLpBFR—were paired for their US and MRI assessments at both pre-test and post-test. For instance, TRAD1 was paired with LLpBFR1, TRAD2 with LLpBFR2, and so forth, ensuring that measurements were taken in a consistent and controlled manner. Post-intervention measurements of all dependent variables were conducted in the same manner as the pre-test, with all completed within two weeks following 1 week after last training session.

Table 12. Data collection procedures

	Signing consent form	DVT screening questionnaire	General health check	Isometric strength test	IRM strength test	ABI test	Muscle thickness test (US)	Muscle CSA test (MRI)	Resistance training
W0	✓	✓	✓	✓	✓	✓	✓	✓	
W1									✓
W2									✓
W3				✓	✓				✓
W4									✓
W5									✓
W6									✓
W7-8				✓	✓	✓	✓	✓	

Data Analyses

The statistical analysis was carried out using IBM SPSS Statistics version 20. Baseline characteristics of participants were reported using descriptive statistics, specifically mean and standard deviation. Pre-test data were grouped into five aspects: Anthropometrics, Physiological Measurements, Biceps Brachii Morphologies, Vastus Lateralis Morphologies, and Vastus lateralis architectures and compared by using Multivariate Analysis of Variance (MANOVA) to find out any significant difference between group at baseline.

Changes in muscle thickness (cm), muscle cross-sectional area (mm^2), muscle isometric strength (newtons), muscle dynamic strength (kg and lbs), strength: body weight ratio (N/kg), fascicle angle (degree), fascicle length (mm), and fascia thickness (cm), ankle-brachial index (ABI) from pre-training to post-training were analyzed using a paired-sample t-test. Absolute change was calculated with 95% Confidence Interval. Between-group comparisons of post-test values for Biceps brachii morphologies, Vastus lateralis morphologies, Vastus lateralis architectures, and Physiologies difference were conducted using MANOVA to identify significant differences between the two training protocols.

Validity

To ensure the validity of the training program, the details were assessed by three external, highly qualified sport science specialists (Appendix C). This evaluation thoroughly examined various aspects of the training program, including the warm-up protocol, exercise selection, exercise order, repetition duration, rest intervals between sets, progression model, training intensity, appropriateness of blood flow restriction, and overall suitability for achieving our research objectives.

The index of objective congruence

The index of objective congruence (IOC) score was determined by three external experts in the field. An expert in the field of sport and exercise science or medical science related to exercise is distinguished by 1) holding a Ph.D. in a relevant discipline, such as sport science or medical science, 2) demonstrating a comprehensive understanding of both theory and practice, 3) serving as a university lecturer or professor, and 4) actively contributing to academic knowledge through peer-reviewed publications and participating in conferences. Additionally, they possess extensive professional knowledge of resistance training methods and techniques, including strength and hypertrophy

The IOC for each component of the training program is as follows: the warm-up protocol scored 0.89, exercise selections received a perfect score of 1, and the order of exercises scored 0.67. Repetition durations were rated at 0.67, while the rest interval between sets achieved a score of 1. Training volume, the number of repetitions per set, the progression model, and the intensity of training each received a score of 1. The blood flow restriction technique was rated 0.67, and training time received a perfect score of 1. These scores highlight areas of both consensus and potential improvement in the training protocol.

Reliability

To measure strength, the test-retest reliability of the ISOFORCE isokinetic machine was demonstrated in a previous study by Mau-Moeller et al. (2017). The results showed excellent reliability for different muscle groups and testing protocols. For intrasession reliability of knee extensor strength testing, the intraclass correlation coefficient (ICC) of peak torque at 60, 120, and 180 degrees per second was 0.99, 0.99, and 0.99, respectively. The ICC for maximum voluntary isometric contraction testing of knee extensors was 0.97. Similarly, for intrasession reliability of knee flexor strength testing, the ICC of peak torque at 60, 120, and 180 degrees per second was 0.99, 0.99, and 0.99, respectively, and the ICC for maximum voluntary isometric contraction of knee flexors was 0.98. Overall, the ISOFORCE isokinetic machine appears to be a highly reliable tool for strength testing.

For measuring muscle thickness, B-mode ultrasound is the most popular method in previously published studies. Its reliability is well-recognized in many hypertrophy studies. For example, the test-retest ICC of B-mode ultrasound was reported to be excellent, ranging from 0.97 to 0.98 in Amirthalingam et al. (2016), 0.98 to 0.99 in Schoenfeld et al. (2016), 0.99 in Zaroni et al. (2018), 0.93 to 0.98 in Barbalho et al. (2020), and 0.96 in Hirono et al. (2020). Overall, B-mode ultrasound appears to be a very reliable tool for hypertrophy testing.

CHAPTER 4
RESULTS

In this chapter, the researcher reported the findings in order to answer the research objectives which were:

1) To compare changes in the muscle thickness and muscle cross-sectional area of the vastus lateralis and biceps brachii from pre-test to post-test within and between groups.

2) To compare changes in the architecture of the vastus lateralis from pre-test to post-test within and between groups.

3) To compare changes in dynamic strength and isometric strength from pre-test to post-test within and between groups.

4) To compare changes in the ankle brachial index score from pre-test to post-test within and between groups.

The flowchart of study from recruitment to final analysis was showed as followed:

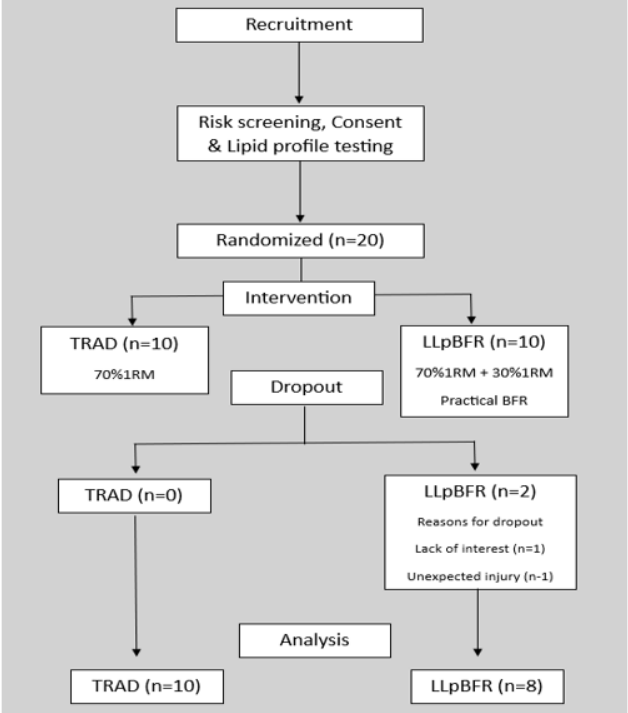


Figure 34. Flowchart of the study.

The results would be divided into 11 parts and reported as followed:

4.1 **Participants' baseline characteristics**: The descriptive statistics: mean ($\bar{x}$) and standard deviation (S.D.), showing participants' baseline characteristics and inferential statistics, MANOVA, comparing between-group difference.

4.2 **Change in muscle thickness and muscle cross-sectional area**: The inferential statistics, Paired-sample t-test, comparing pre-to-post changes within group.

4.3 **Biceps brachii morphologies difference**: The inferential statistics, MANOVA, comparing between groups difference.

4.4 **Vastus lateralis morphologies difference**: The inferential statistics, MANOVA, comparing between groups difference.

4.5 **Change in Vastus lateralis architecture**: The inferential statistics, Paired-sample t-test, comparing pre-to-post changes within group.

4.6 **Vastus lateralis architecture difference**: The inferential statistics, MANOVA, comparing between groups difference.

4.7 **Change in isometric and dynamic strength**: The inferential statistics, Paired-sample t-test, comparing pre-to-post changes within group.

4.8 **Change in ankle-brachial index**: The inferential statistics, Paired-sample t-test, comparing pre-to-post changes within group.

4.9 **Change in strength: body weight ratio**: The inferential statistics, Paired-sample t-test, comparing pre-to-post changes within group.

4.10 **Physiologies difference**: The inferential statistics, MANOVA, comparing physiological change difference between groups.

4.11 **Rate of perceived exertion different**: The inferential statistics, MANOVA, comparing rata of perceived exertion difference between groups.

Symbols and abbreviations for data analysis and interpretation

In analyzing and interpreting the data, the researcher has defined the following symbols and abbreviations used in presenting the results as followed:

n = the number of participants.

$\bar{x}$ = the mean (average).

S.D. = the standard deviation.

t = the t-statistic used in t-distribution.

F = the F-statistic used in F-distribution.

η_2^p = the effect size measured for one-way ANOVA

Box's M = Box's M statistic, which assesses the equality of covariance matrices in multivariate analysis of variance (MANOVA).

df1 = the degrees of freedom associated with the numerator of the F-ratio in statistical tests.

df2 = the degrees of freedom associated with the denominator of the F-ratio in statistical tests.

Approx. Chi-Square = the approximate chi-square value.

Hotelling's Trace = a key statistical metric utilized MANOVA.

p = the probability value in hypothesis testing.

* = statistical significance at the 0.05 level.

95% CI = 95% Confidence Interval

Pre = the pre-training test.

Post = the post-training test.

Group = the training methods, divided into two groups:

TRAD = Control Group.

LLpBFR = Experimental Group.

These symbols and abbreviations are used consistently throughout the presentation of the data analysis results.

4.1 Participants' baseline characteristics and training details

The following table displayed the anthropometric, physiological, and morphological variables of the control group (TRAD) and the experimental group (LLpBFR).

Table 13. Participants' characteristics at baseline

	TRAD(n=10) $\bar{x}$± S.D.	LLpBFR(n=8) $\bar{x}$± S.D.	*F*	*p*-value	MANOVA
Anthropometries					Hotelling's Trace = .691
Height (cm)	174.90±5.32	173.13±5.54	.477	.500	
Body mass (kg)	69.00±11.90	68.5±11.35	.008	.929	
Physiologies					Hotelling's Trace = .929
1RM leg extension (lbs)	142±19.89	153.75±39.98	.666	.427	
1RM preacher curl (kg)	31.50±11.07	38.75±13.82	1.532	.234	
Isometric knee extension (N)	229.10±57.51	239.88±62.91	.144	.710	
Isometric elbow flexion (N)	43.90±12.55	48.63±10.29	.735	.404	
ISO knee extension strength: body weight ratio (N/kg)	3.39±0.90	3.57±1.02	.153	701	
ISO elbow flexion strength: body weight ratio (N/kg)	0.65±0.21	0.73±0.21	.600	.450	
ABI (A.U.)	1.09±0.10	1.16±0.15	1.404	.253	
Biceps brachii morphologies					Hotelling's Trace = .709
MT BB$_{\text{proximal}}$ (cm)	2.17±0.27	2.20±0.27	.057	.815	
MT BB$_{\text{middle}}$ (cm)	1.96±0.26	1.92±0.27	.121	.732	
MT BB$_{\text{distal}}$ (cm)	1.86±0.21	1.93±0.35	.271	.610	
MA BB$_{\text{proximal}}$ (mm^2)	772.60±131.96	723.63±128.53	.626	.440	
MA BB$_{\text{middle}}$ (mm^2)	819.00±130.46	710.25±186.97	2.114	.165	
MA BB$_{\text{distal}}$ (mm^2)	843.10±139.86	797.75±197.32	.326	.576	
Vastus lateralis morphologies					Hotelling's Trace = .838
MT VL$_{\text{proximal}}$ (cm)	2.76±0.57	2.54±0.65	.585	.456	
MT VL$_{\text{middle}}$ (cm)	2.10±0.33	2.24±0.56	.459	.508	
MT VL$_{\text{distal}}$ (cm)	1.96±0.41	2.08±0.65	.255	.620	
MA VL$_{\text{proximal}}$ (mm^2)	2489.40±381.71	2782.38±794.03	1.066	.317	

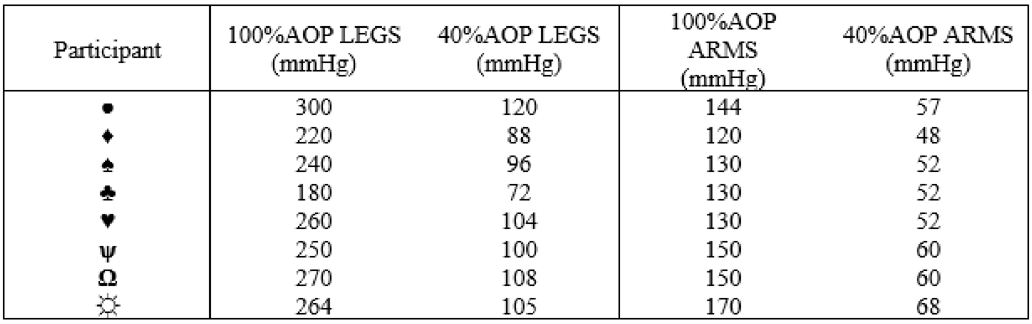
MA VL $_{\text{middle}}$ (mm^2)	2562.20±376.54	2704.04±628.89	.356	.559	
MA VL $_{\text{distal}}$ (mm^2)	1587.30±296.01	1695.63±383.73	.459	.508	
Vastus lateralis architectures					Hotelling's Trace = .539
Fascicle angle (degree)	15.55±5.03	14.51±3.15	.259	.618	
Fascicle length (mm)	71.98±10.76	74.01±10.31	.165	.690	
Fascia thickness (cm)	1.26±0.46	0.98±0.34	2.156	.161	

Data were reported as mean ± standard deviation. Abbreviation; N=Newtons; MT=muscle thickness; MA=muscle cross-sectional area; BB=biceps brachii; VL=vastus lateralis; ISO=Isometric, N/kg=Newton per kilogram 1RM=1repetition maximum; mm^2=square millimeters; A.U.=arbitrary unit; ABI = Ankle-brachial index.

Multivariate analysis of variance (MANOVA) was conducted to compare participants at baselines via 5 aspects: Anthropometries, Physiologies, Biceps brachii morphologies, Vastus lateralis morphologies, and Vastus lateralis architectures. It was demonstrated that there were no statistically significant differences between the groups at any aspects (p>.05).

Specifically, at baseline, there were no significant differences between groups in any aspect, as indicated by Hotelling's Trace: Anthropometries (.691), Physiologies (.929), Biceps brachii morphologies (.709), Vastus lateralis morphologies (.838), and Vastus lateralis architecture (.539).

Table 14. Arterial occlusion pressure at 100% and 40% of individual participants in LLpBFR



Participant	100%AOP LEGS (mmHg)	40%AOP LEGS (mmHg)	100%AOP ARMS (mmHg)	40%AOP ARMS (mmHg)
●	300	120	144	57
♦	220	88	120	48
♠	240	96	130	52
♣	180	72	130	52
♥	260	104	130	52
ψ	250	100	150	60
Ω	270	108	150	60
☼	264	105	170	68

From table 14, before training experiment began, participants were measured for their arterial occlusion pressure (AOP) by clinical pneumatic cuffs and 40% of value were calculated, individually. The findings were that the average 40%AOP of legs was 98.9±14.4 mmHg while the average 40%AOP of arms was 55.7±6.4 mmHg.

Table 15.Numbers of repetitions performed in each week

Week	Preacher curl 70%1RM sets x̄± S.D.	Preacher curl 30%1RM pBFR sets x̄± S.D.	Knee extension 70%1RM sets x̄± S.D.	Knee extension 30%1RM pBFR sets x̄± S.D.
1	9.5±5.3	23.5±7.9	12.9±5.3	32.9±14.3
2	11.3±5.7	24.0±7.7	14.4±5.2	40.3±16.6
3	10.6±5.5	28.0±11.0	13.0±5.0	42.0±27.9
4	9.3±4.3	29.2±8.4	12.2±3.6	44.5±23.8
5	13.5±6.2	35.5±13.9	14.1±3.8	49.8±22.0
6	14.7±5.9	36.0±8.0	15.8±3.8	51.9±27.2

Table 15 displayed the weekly average repetition counts. Across the six weeks, high-intensity sets for preacher curls and knee extensions averaged 11.5±2.2 and 13.7±1.3 repetitions respectively. In contrast, low-intensity sets with practical blood flow restriction averaged 29.4±5.4 and 43.6±6.9 repetitions for preacher curls and knee extensions respectively.

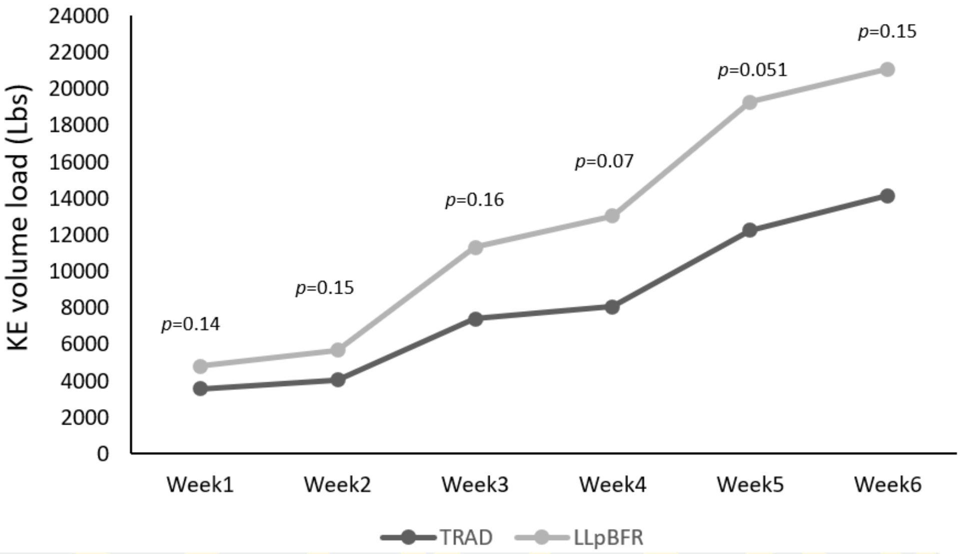


Figure 35. Average volume load from knee extension (KE) exercise from week 1

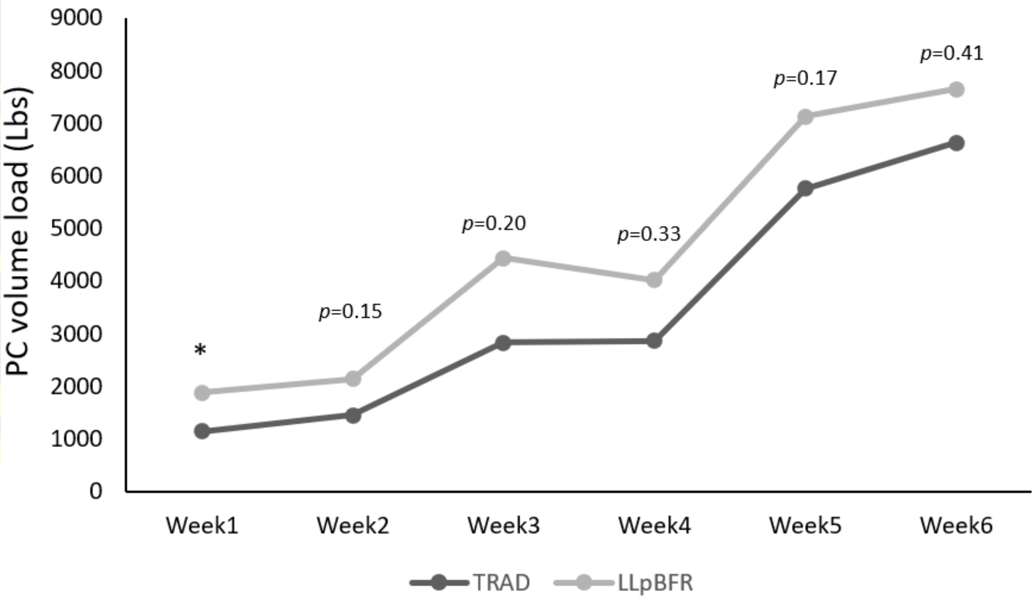


Figure 36. Average volume load from preacher curl (PC) exercise from week 1-6, * indicates p<.05, significant different between groups.

From figure 35 and 36, volume loads of exercises, as calculated by volume load = set x rep x load, displayed weekly. Across the six weeks, the average volume loads for knee extension exercise in TRAD were 3575lbs, 4067lbs, 7403lbs, 8061lbs, 12257lbs, and 14159lbs from week 1-6, respectively. Similarly, the average volume loads for knee extension exercise in LLpBFR were 4792lbs, 5680lbs, 11331lbs, 13048lbs, 19279lbs, and 21091lbs, respectively.

For preacher curl, the average volume loads for TRAD were 1147lbs, 1449lbs, 2826lbs, 2870lbs, 5754lbs, and 6626lbs and for LLpBFR were from week 1-6, respectively. Independent samples t-test statistics demonstrated that there was significant different between groups of average volume load of preacher curl at week 1 (p=0.04).

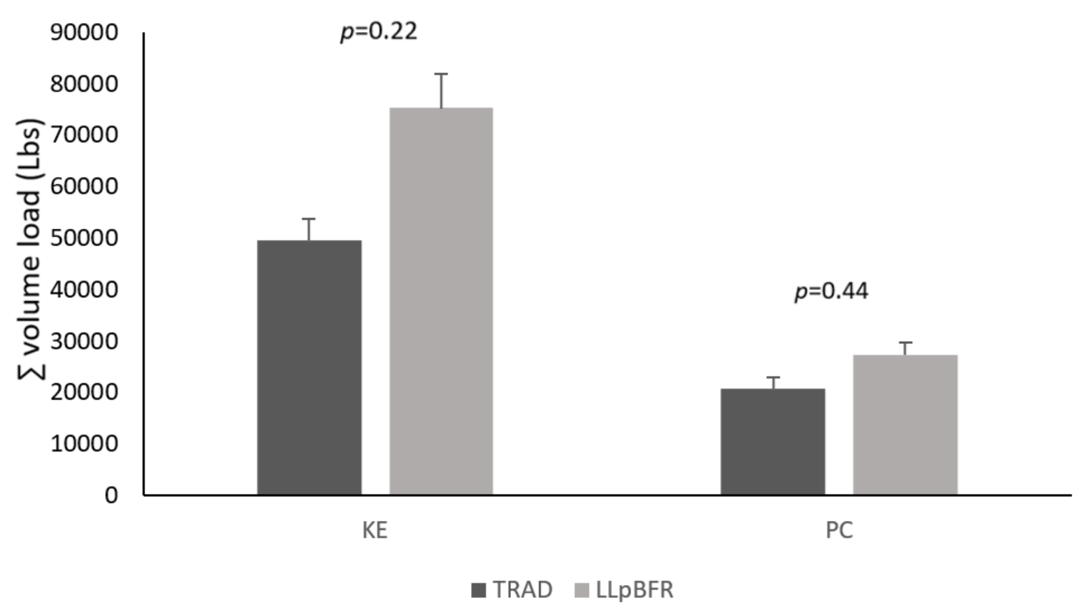


Figure 37. Means and standard deviations of sum of volume loads from 6-week training of knee extension (KE) and preacher curl (PC) exercises.

From 6-week training, the participants in TRAD group trained for total 49,522±4,267lbs of knee extension exercise and 20,672±2,255lbs of preacher curl exercise, respectively. Similarly, the participants in LLpBFR group trained for total 75,221±6,743lbs and 27,243±2,424lbs of knee extension and preacher curl exercises, respectively. No significant difference between group was observed.

4.2 Change in muscle thickness and muscle cross-sectional area

The following tables displayed the pre-to-post changes in muscle thickness and muscle cross-sectional area of the control group (TRAD) and the experimental group (LLpBFR).

4.2.1 Changes in muscle thickness of Biceps brachii and Vastus lateralis muscles at proximal, middle, and distal regions of the control group (TRAD)

Table 16. Changes in muscle thickness via ultrasound imaging assessment

Regions	Pre x̄± S.D.	Post x̄± S.D.	□ (95% CI)	*t*	*df*	Sig(2-tailed)
MT BB$_{proximal}$ (cm.)	2.17±0.27	2.28±0.15	0.11(0.09;0.31)	1.218	9	.254
MT BB$_{middle}$ (cm.)	1.96±0.26	2.41±0.24*	0.45(0.20;0.71)	4.064	9	.003
MT BB$_{distal}$ (cm.)	1.86±0.21	2.33±0.28*	0.47(0.28;0.67)	5.583	9	.000
MT VL$_{proximal}$ (cm.)	2.76±0.57	2.94±0.43	0.18(-0.32;0.67)	0.801	9	.444
MT VL$_{middle}$ (cm.)	2.10±0.33	2.42±0.22*	0.32(0.08;0.58)	2.940	9	.016
MT VL$_{distal}$ (cm.)	1.96±0.41	2.25±0.35*	0.29(0.15;0.44)	4.567	9	.001

Data were reported as mean ± standard deviation. Abbreviation; MT=muscle thickness; BB=biceps brachii; VL=vastus lateralis.

From table 16, Paired-sample t-test was conducted to compare pre-to-post changes of Biceps brachii and Vastus lateralis muscle thickness at proximal, middle, and distal regions.

It was showed that at Pre (week 0), muscle thickness of biceps brachii at proximal, middle, and distal regions were 2.17±0.27cm, 1.96±0.26cm, and 1.86±0.21cm, respectively. Similarly, muscle thickness of vastus lateralis at proximal, middle, and distal regions were 2.76±0.57cm, 2.10±0.33cm, 1.96±0.41cm, respectively.

After finishing 6-week training of TRAD group, the results showed that muscle thickness of biceps brachii at proximal, middle, and distal regions increased up to

2.28±0.15cm, 2.41±0.24cm, and 2.33±0.28cm, respectively. In the same way, muscle thickness of vastus lateralis at proximal, middle, and distal regions increased up to 2.94±0.43cm, 2.42±0.22cm, and 2.25±0.35cm, respectively.

Paired-sample t-test statistics demonstrated that for biceps brachii, muscle thickness significantly increased from baseline at only middle region (□0.45, CI$_{95\%}$ = 0.20-0.71, *t* = 4.064, *p* = .003) and distal region (□0.47, CI$_{95\%}$ = 0.28-0.67, *t* = 5.583, *p* = .000). For vastus lateralis, muscle thickness significantly increased from baseline at only middle region (□0.32, CI$_{95\%}$ = 0.08;0.58, *t* = 2.940, *p* = .016) and distal region (□0.29, CI$_{95\%}$ = 0.15-0.44, *t* = 4.567, *p* = .001).

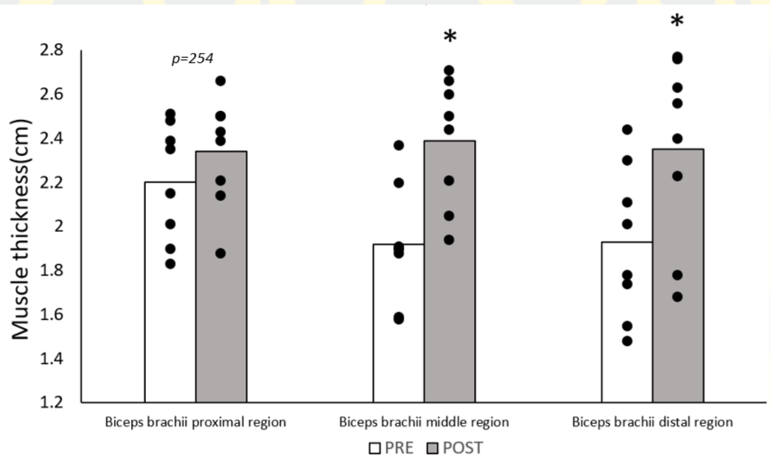


Figure 38. Biceps brachii thickness at Pre and Post (TRAD). * indicates p<.05 compared to Pre.

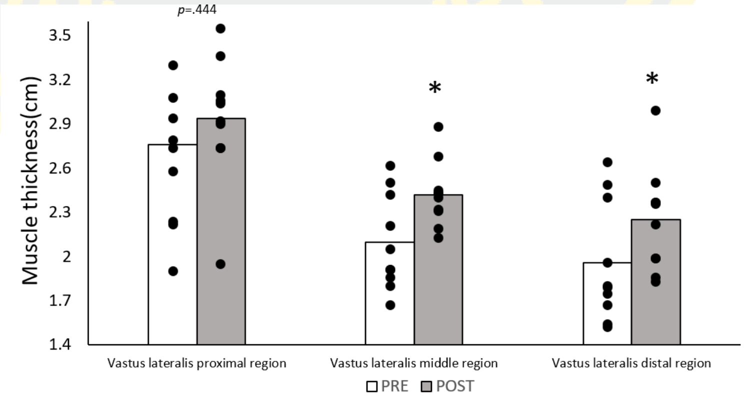


Figure 39. Vastus lateralis thickness at Pre and Post (TRAD). * indicates p<.05 compared to Pre

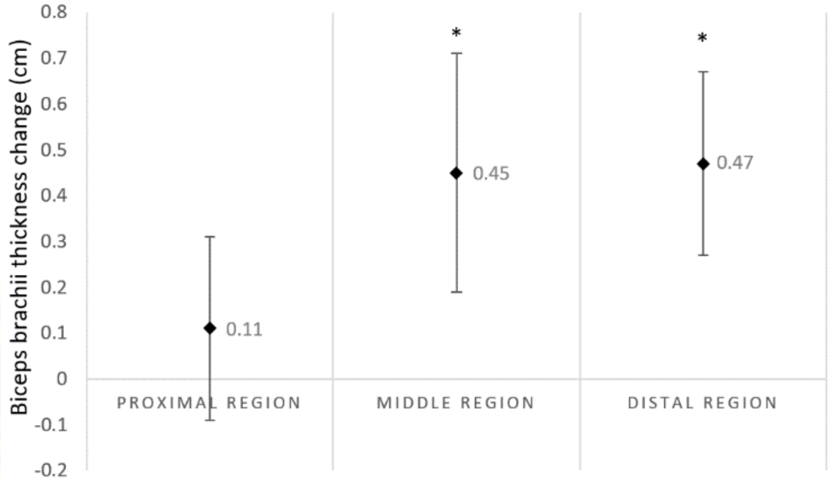


Figure *40*. Change in Biceps brachii thickness in TRAD with 95%CI, * indicates p<.05 compare to Pre.

Figure 41. Change in Vastus lateralis thickness in TRAD with 95%CI, * indicates p<.05 compare to Pre.

4.2.2 Changes in muscle thickness of Biceps brachii and Vastus lateralis muscles at proximal, middle, and distal regions of the experimental group (LLpBFR)

Table 17. Changes in muscle thickness via ultrasound imaging assessment

Sites	Pre x̄± S.D.	Post x̄± S.D.	□ (95% CI)	t	df	Sig(2-tailed)
MT BB$_{proximal}$ (cm.)	2.20±0.27	2.34±0.25	0.13(-0.07;0.34)	1.592	7	.156
MT BB$_{middle}$ (cm.)	1.92±0.27	2.39±0.29*	0.47(0.27;0.68)	5.465	7	.001
MT BB$_{distal}$ (cm.)	1.93±0.35	2.35±0.42*	0.42(0.15;0.70)	3.612	7	.009
MT VL$_{proximal}$ (cm.)	2.54±0.65	3.17±0.84*	0.63(0.17;1.09)	3.340	7	.014
MT VL$_{middle}$ (cm.)	2.24±0.56	2.54±0.45	0.30(-0.07;0.68)	1.932	7	.095
MT VL$_{distal}$ (cm.)	2.08±0.65	2.44±0.46*	0.36(0.02;0.70)	2.494	7	.041

Data were reported as mean ± standard deviation. Abbreviation; MT=muscle thickness; BB=biceps brachii; VL=vastus lateralis.

From table 17, Paired-sample t-test was conducted to compare pre-to-post changes of Biceps brachii and Vastus lateralis muscle thickness at proximal, middle, and distal regions.

It was showed that at Pre (week 0), muscle thickness of biceps brachii at proximal, middle, and distal regions were 2.20±0.27cm, 1.92±0.27cm, and 1.93±0.35cm, respectively. Similarly, muscle thickness of vastus lateralis at proximal, middle, and distal regions were 2.54±0.6cm, 2.24±0.56cm, and 2.08±0.65cm, respectively.

After finishing 6-week training of LLpBFR group, the results showed that muscle thickness of biceps brachii at proximal, middle, and distal regions increased up to 2.34±0.25cm, 2.39±0.29cm, and 2.35±0.42cm, respectively. In the same way, muscle thickness of vastus lateralis at proximal, middle, and distal regions increased up to 3.17±0.84cm, 2.54±0.45cm, and 2.44±0.46cm, respectively.

Paired-sample t-test statistics demonstrated that for biceps brachii, muscle thickness significantly increased from baseline at only middle region (□0.47, CI$_{95\%}$ = 0.27-0.68, t = 5.465, p = .001) and distal region (□0.42, CI$_{95\%}$ = 0.15-0.70, t = 3.612, p = .009).

For vastus lateralis, muscle thickness significantly increased from baseline at only proximal region (□0.63, $CI_{95\%} = 0.17\text{-}1.09$, $t = 3.340$, $p = .014$) and distal region (□0.30, $CI_{95\%} = 0.02\text{-}0.70$, $t = 2.494$, $p = .041$).

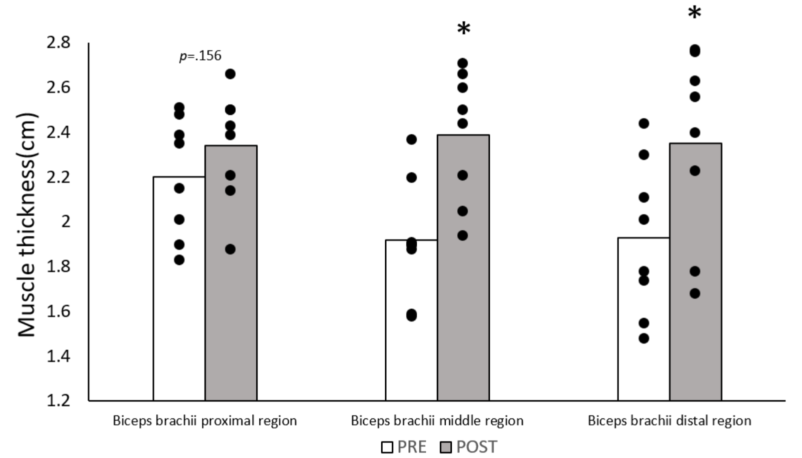


Figure 42. Biceps brachii thickness at Pre and Post (LLpBFR). * indicates $p < .05$ compared to Pre

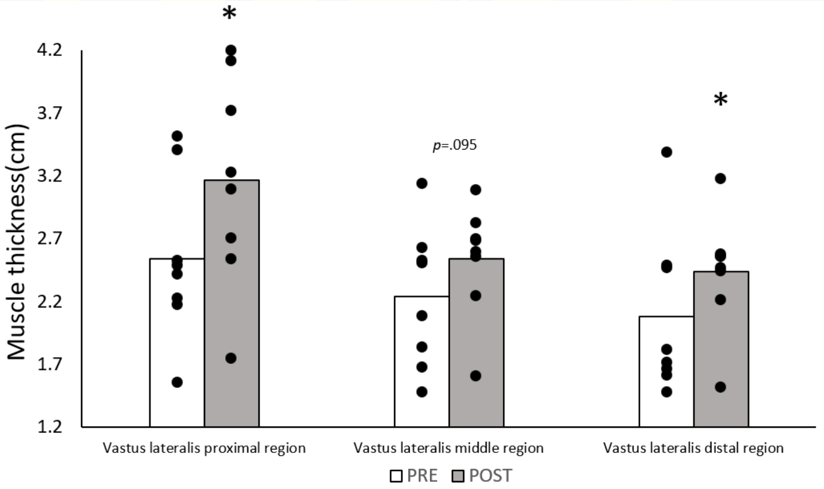


Figure 43. Vastus lateralis thickness at Pre and Post (LLpBFR). * indicates $p < .05$ compared to Pre

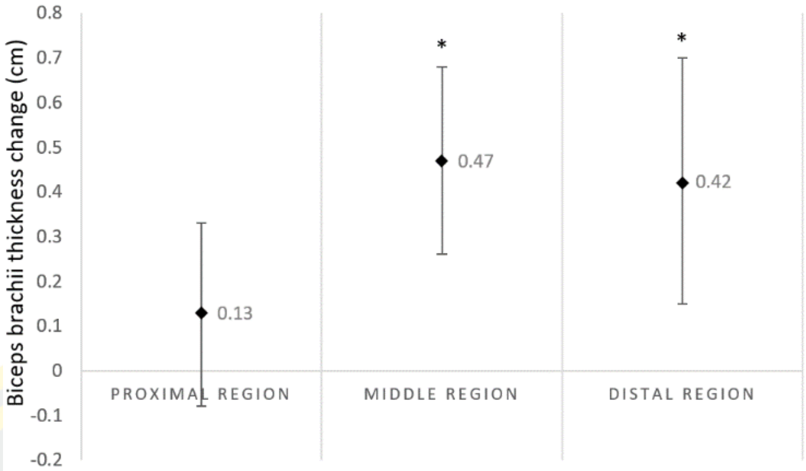


Figure 44. Change in Biceps brachii thickness in LLpBFR with 95%CI, * indicates p<.05 compare to Pre.

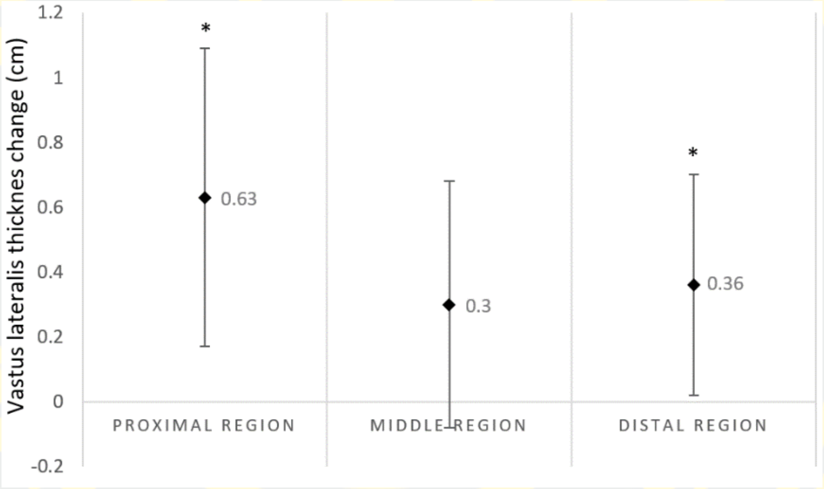


Figure 45. Change in Vastus lateralis thickness in LLpBFR with 95%CI, * indicates p<.05 compare to Pre.

4.2.3 Changes in muscle cross-sectional area of Biceps brachii and Vastus lateralis muscles at proximal, middle, and distal regions of the control group (TRAD)

Table 18. Changes in muscle cross-sectional area via MRI assessment

Sites	Pre $\bar{x}$± S.D.	Post $\bar{x}$± S.D.	□ (95% CI)	*t*	*df*	Sig(2-tailed)
MA $BB_{proximal}$ (mm^2)	772.60 ±131.96	836.40 ±146.15*	63.80 (4.41;123.19)	2.430	9	.038

MA BB_{middle} (mm^2)	819.00 ±130.46	860.20 ±142.59*	41.20 (17.44;64.96)	3.922	9	.004
MA BB_{distal} (mm^2)	843.10 ±139.86	945.50 ±168.13*	102.40 (61.69;143.11)	5.690	9	000
MA $VL_{proximal}$ (mm^2)	2489.40 ±381.71	2775.40 ±598.27*	286.00 (37.32;534.68)	2.602	9	.029
MA VL_{middle} (mm^2)	2562.20 ±376.54	2784.50 ±361.52*	222.30 (62.47;382.13)	3.146	9	.012
MA VL_{distal} (mm^2)	1587.30 ±296.01	1809.90 ±349.14*	222.60 (40.38;404.37)	2.770	9	.022

Data were reported as mean ± standard deviation. Abbreviation; MA=muscle cross-sectional area; BB=biceps brachii; VL=vastus lateralis.

From table 18, Paired-sample t-test was conducted to compare pre-to-post changes of Biceps brachii and Vastus lateralis muscle cross-sectional area at proximal, middle, and distal regions.

It was showed that at Pre (week 0), muscle cross-sectional area of biceps brachii at proximal, middle, and distal regions were 772.6±131.96mm^2, 819.00±130.46mm^2, and 843.10±139.86mm^2, respectively. Similarly, muscle cross-sectional area of vastus lateralis at proximal, middle, and distal regions were 2489.40±381.71mm^2, 2562.20±376.54mm^2, 1587.30±296.01mm^2, respectively.

After finishing 6-week training of TRAD group, the results showed that muscle cross-sectional area of biceps brachii at proximal, middle, and distal regions increased up to 836.40±146.15mm^2, 860.20±142.59mm^2, and 945.50±168.13mm^2, respectively. In the same way, muscle cross-sectional area of vastus lateralis at proximal, middle, and distal regions increased up to 2775.40±598.27mm^2, 2784.50±361.52mm^2, and 1809.90±349.14mm^2, respectively.

Paired-sample t-test statistics demonstrated that for biceps brachii, muscle cross-sectional area significantly increased from baseline at proximal region (□63.80, $CI_{95\%}$ = 4.41-123.19, t = 2.430, p = .038), middle region (□41.20, $CI_{95\%}$ = 17.44-64.96, t = 3.922, p = .004) and distal region (□102.40, $CI_{95\%}$ = 61.69-143.11, t = 5.690, p = .000). For vastus lateralis, muscle cross-sectional area significantly increased from baseline at proximal region (□268.00, $CI_{95\%}$ = 37.32-534.68, t = 2.602, p = .029), middle region (□222.30, $CI_{95\%}$ = 62.47-382-13, t = 3.146, p = .012) and distal region (□222.60, $CI_{95\%}$ = 40.38-404.37, t = 2.770, p = .022).

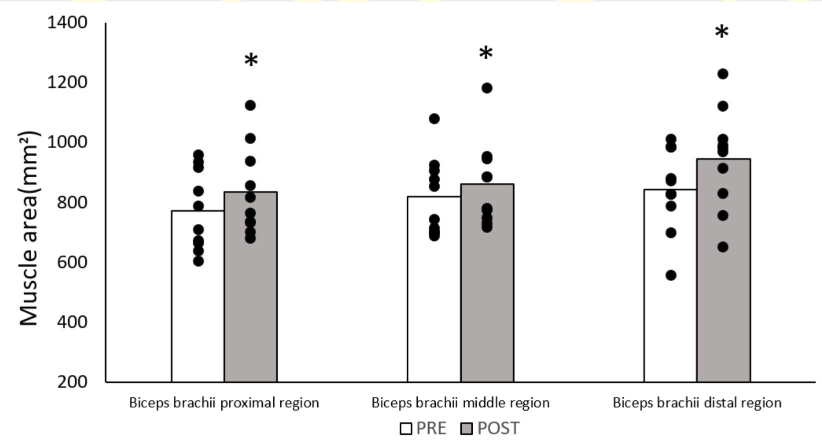


Figure 46. Biceps brachii cross-sectional area at Pre and Post (TRAD). * indicates p<.05 compared to Pre

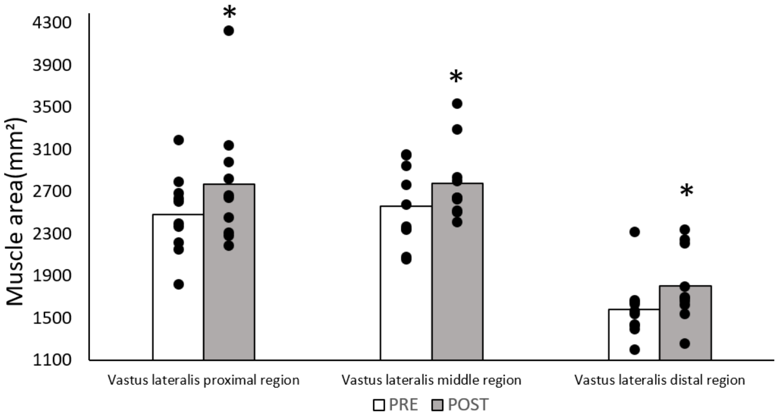


Figure 47. Vastus lateralis cross-sectional area at Pre and Post (TRAD). * indicates p<.05 compared to Pre

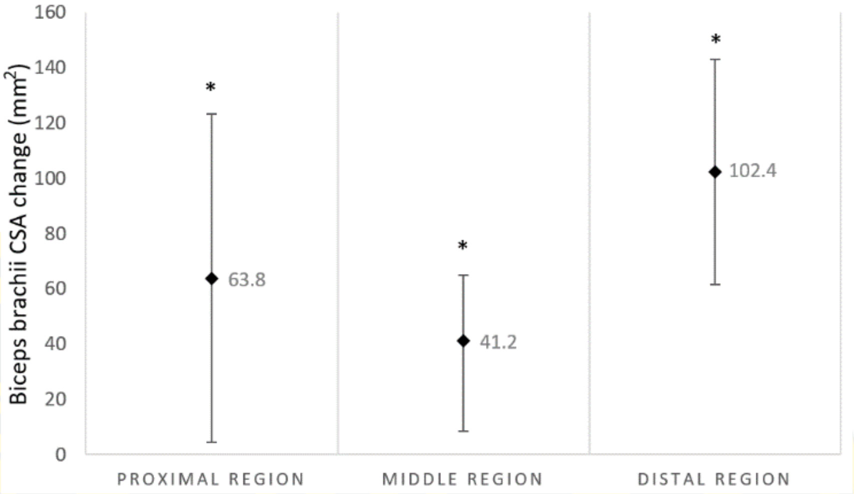


Figure *48*. Change in Biceps brachii cross-sectional area in TRAD with 95%CI, * indicates p<.05 compare to Pre

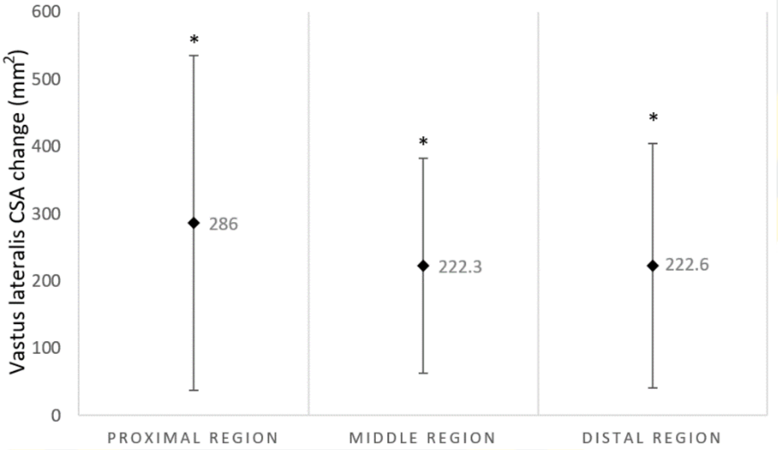


Figure 49. Change in Vastus lateralis cross-sectional area in TRAD with 95%CI, * indicates p<.05 compare to Pre.

4.2.4 Changes in muscle cross-sectional area of Biceps brachii and Vastus lateralis muscles at proximal, middle, and distal regions of the experimental group (LLpBFR)

Table 19. Changes in muscle cross-sectional area via MRI assessment

Sites	Pre $\bar{x}$± S.D.	Post $\bar{x}$± S.D.	□ (95% CI)	*t*	*df*	Sig(2-tailed)
MA BB$_{proximal}$ (mm^2)	723.63 ±128.53	788.88 ±164.46*	65.25 (26.45;104.05)	3.977	7	.005
MA BB$_{middle}$ (mm^2)	710.25 ±186.97	766.50 ±190.31*	56.25 (29.29;83.21)	4.924	7	.002
MA BB$_{distal}$ (mm^2)	797.75 ±197.32	932.75 ±190.68*	135.00 (48.88;221.21)	3.707	7	.008
MA VL$_{proximal}$ (mm^2)	2782.38 ±794.03	3083.00 ±796.55*	255.63 (148.16;363.09)	5.625	7	.001
MA VL$_{middle}$ (mm^2)	2704.04 ±628.89	2950.13 ±632.99*	245.63 (61.97;429.28)	3.163	7	.016
MA VL$_{distal}$ (mm^2)	1695.63 ±383.73	1910.63 ±402.58*	215.00 (112.19;317.81)	4.945	7	.002

Data were reported as mean ± standard deviation. Abbreviation; MT=muscle thickness; BB=biceps brachii; VL=vastus lateralis.

From table 19, Paired-sample t-test was conducted to compare pre-to-post changes of Biceps brachii and Vastus lateralis muscle cross-sectional area at proximal, middle, and distal regions.

It was showed that at Pre (week 0), muscle cross-sectional area of biceps brachii at proximal, middle, and distal regions were 723.63±128.53mm^2, 710.25±186.97mm^2, and 797.75±197.32mm^2, respectively. Similarly, muscle cross-sectional area of vastus lateralis at proximal, middle, and distal regions were 2782.38±794.03 mm^2, 2704.04±628.89 mm^2, and 1695.63±383.73 mm^2, respectively.

After finishing 6-week training of LLpBFR group, the results showed that muscle cross-sectional area of biceps brachii at proximal, middle, and distal regions increased up to 788.88±164.46mm^2, 766.50±190.31mm^2, and 932.75±190.68mm^2, respectively. In the same way, muscle cross-sectional area of vastus lateralis at proximal, middle, and distal regions increased up to 3083.00±796.55mm^2, 2950.13±632.99mm^2, and 1910.63±402.58mm^2, respectively.

Paired-sample t-test statistics demonstrated that for biceps brachii, muscle cross-sectional area significantly increased from baseline at proximal region (□65.25, $CI_{95\%}$ = 26.45-104.05, t = 3.977, p = .005), middle region (□56.25, $CI_{95\%}$ = 20.2-83.32, t = 4.924, p = .002) and distal region (□135.00, $CI_{95\%}$ = 48.88-221.21, t = 3.707, p = .008). For vastus lateralis, muscle cross-sectional area significantly increased from baseline at proximal region (□255.63, $CI_{95\%}$ = 148.16-363.09, t = 5.625, p = .001), middle region (□245.63, $CI_{95\%}$ = 61.97-429.28, t = 3.163, p = .016) and distal region (□215.00, $CI_{95\%}$ = 112.19-317.81, t = 4.945, p = .002).

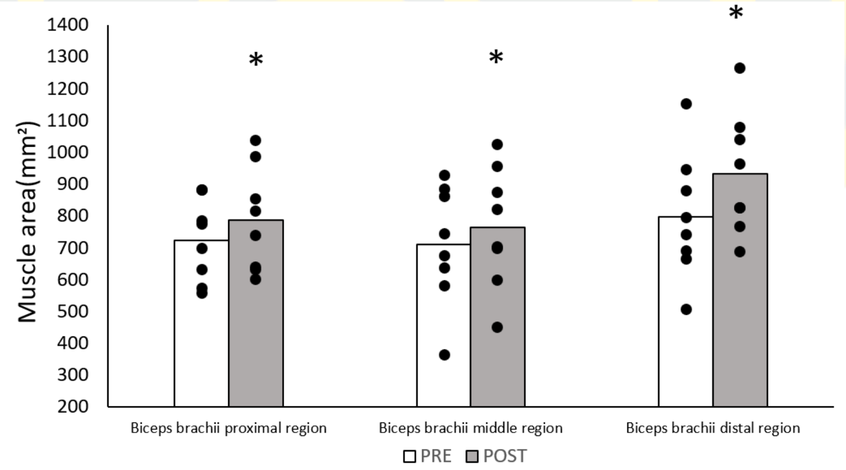


Figure 50. Biceps brachii cross-sectional area at Pre and Post (LLpBFR). * indicates p<.05 compared to Pre.

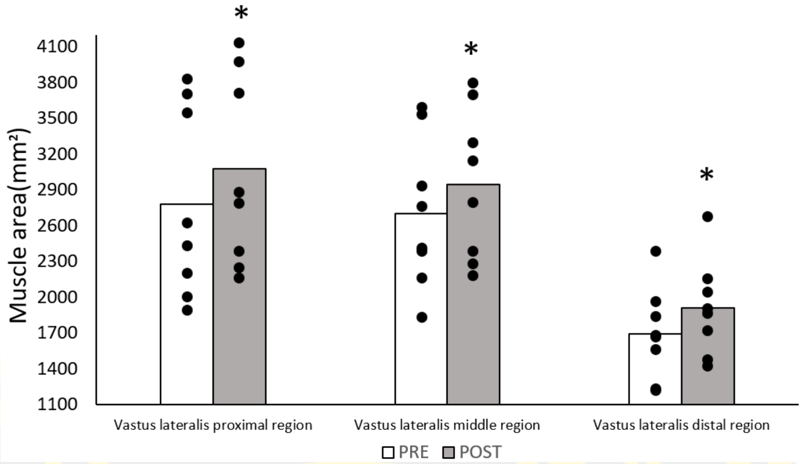


Figure 51. Vastus lateralis cross-sectional area at Pre and Post (LLpBFR). * indicates p<.05 compared to Pre

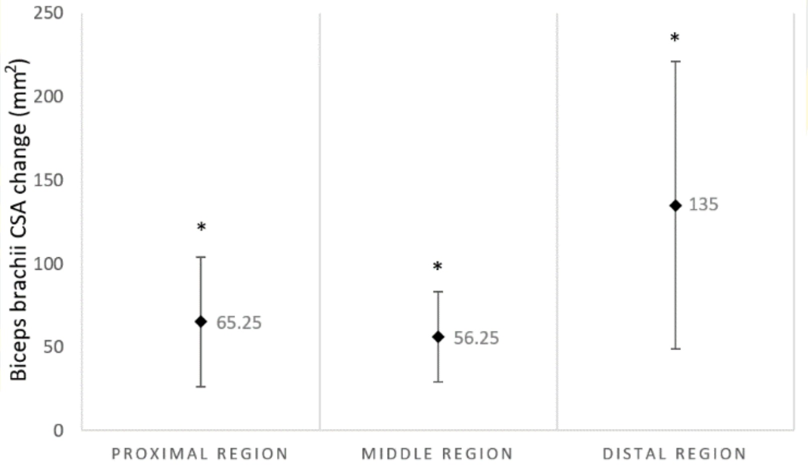


Figure 52. Change in Biceps brachii cross-sectional area in LLpBFR with 95%CI, * indicates p<.05 compare to Pre.

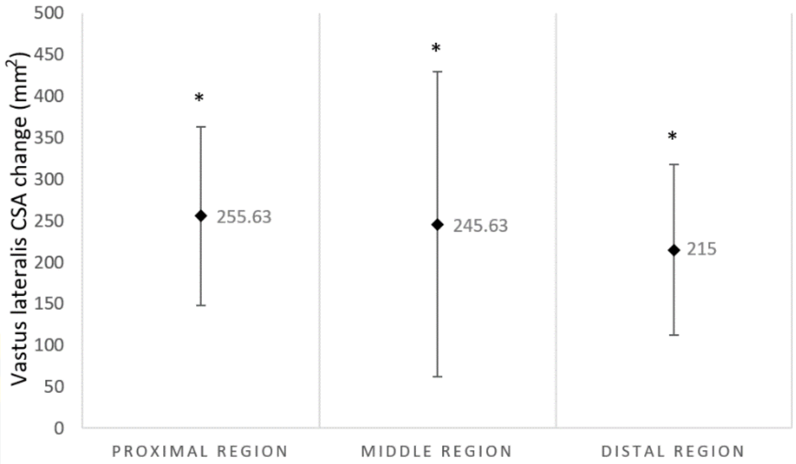


Figure 53. Change in Vastus lateralis cross-sectional area in LLpBFR with 95%CI, * indicates p<.05 compare to Pre.

4.3 Biceps brachii morphologies difference

Table 20. between-group comparison of Biceps brachii morphologies

	Group	x̄	SD.	MANOVA
MT BB$_{proximal}$ (cm)	LLpBFR	2.34	0.25	
	TRAD	2.81	0.15	
	Total	2.30	0.20	
MT BB$_{middle}$ (cm)	LLpBFR	2.39	0.29	Box's M = 47.750 F = 1.294 df1 = 21 df2 = 830.320 Sig. = .170
	TRAD	2.41	0.24	
	Total	2.40	0.25	
MT BB$_{distal}$ (cm)	LLpBFR	2.35	0.42	
	TRAD	2.34	0.28	
	Total	2.34	0.34	
MA BB$_{proximal}$ (mm^2)	LLpBFR	788.88	164.46	Bartlet's Test of Sphericity Approx. Chi-Square = 539.900 df = 20 Sig. = .000
	TRAD	836.40	146.15	
	Total	815.28	151.78	
MA BB$_{middle}$ (mm^2)	LLpBFR	766.50	190.31	
	TRAD	860.20	142.59	
	Total	818.56	167.25	
MA BB$_{distal}$ (mm^2)	LLpBFR	932.75	190.68	
	TRAD	945.50	168.13	
	Total	939.83	173.15	

From table 20, Box's M statistic was calculated to verify the assumptions of multivariate analysis of variance (MANOVA).

The results from the Box's M test indicated that Box's M = 47.750, F = 1.294, and Sig. = .170, which is higher than the significance level (p>.05). This suggests that the covariance matrices are not significantly different from each other, meeting the assumption for multiple analysis of variance.

The Bartlet's Test of Sphericity showed a Chi-square value of 539.000 and Sig. = .000, which is statistically significant, indicating that there is a significant variance between groups. Therefore, the Hotelling's Trace test is appropriate due to its robustness in cases where there are differences in variance between groups.

Table *21*. Multivariate Tests of Biceps brachii morphologies difference

Test Name	Value	F	Hypothesis *df*	Error *df*	*p*
Hotelling's Trace	.256	.469	6.000	11.000	.818

Tests of between-subjects effects

Source	Dependent variable	Type III Sum of Square	*df*	Mean Square	F	Sig.
Group	MT $\text{BB}_{\text{proximal}}$	.015	1	.015	.374	.550
	MT $\text{BB}_{\text{middle}}$	.003	1	.003	.038	.847
	MT $\text{BB}_{\text{distal}}$	.001	1	.001	.007	.933
	MA $\text{BB}_{\text{proximal}}$	10038.336	1	10038.336	.421	.526
	MA $\text{BB}_{\text{middle}}$	39020.884	1	39020.884	1.430	.249
	MA $\text{BB}_{\text{distal}}$	722.500	1	722.500	0.230	.882
Error	MT $\text{BB}_{\text{proximal}}$	.635	16	.040		
	MT $\text{BB}_{\text{middle}}$	1.087	16	.068		
	MT $\text{BB}_{\text{distal}}$	1.956	16	.122		
	MA $\text{BB}_{\text{proximal}}$	381555.275	16	23847.205		
	MA $\text{BB}_{\text{middle}}$	436505.600	16	27281.600		
	MA $\text{BB}_{\text{distal}}$	508924.000	16	31807.750		

From the table 21, analyzing the variance of the Biceps brachii morphologies, it was found that Hotelling's Trace = .256, F = .469, Hypothesis *df* = 6.000, and *p* = .818, which was greater than the specified significance level (0.05). This indicated that there was no statistically significant difference in the effectiveness of the two training programs (TRAD and LLpBFR) in developing Biceps brachii morphologies ($p>.05$).

4.4 Vastus lateralis morphologies difference

Table *22*. Between-group comparison of Vastus lateralis morphologies

	Group	$\bar{x}$	SD.	MANOVA
MT VL$_{proximal}$ (cm.)	LLpBFR	3.17	0.84	
	TRAD	2.94	0.43	
	Total	3.04	0.63	
MT VL$_{middle}$ (cm.)	LLpBFR	2.54	0.44	Box's M = 42.189 F = 1.143 df1 = 21 df2 = 830.320 Sig. = .296
	TRAD	2.42	0.22	
	Total	2.48	0.33	
MT VL$_{distal}$ (cm.)	LLpBFR	2.44	0.46	
	TRAD	2.25	0.35	
	Total	2.33	0.40	
MA VL$_{proximal}$ (mm^2)	LLpBFR	3038.00	796.55	Bartlet's Test of Sphericity Approx. Chi-Square = 586.309 df = 20 Sig. = .000
	TRAD	2775.40	598.27	
	Total	2892.11	684.67	
MA VL$_{middle}$ (mm^2)	LLpBFR	2950.13	632.98	
	TRAD	2784.50	361.32	
	Total	2858.11	491.19	
MA VL$_{distal}$ (mm^2)	LLpBFR	1910.63	402.58	
	TRAD	1809.90	349.14	
	Total	1854.67	365.95	

From table 22, Box's M statistic was calculated to verify the assumptions of multivariate analysis of variance (MANOVA).

The results from the Box's M test indicated that Box's M = 42.189, F = 1.143, and Sig. = .296, which is higher than the significance level ($p>.05$). This suggests that the covariance matrices are not significantly different from each other, meeting the assumption for multiple analysis of variance.

The Bartlet’s Test of Sphericity showed a Chi-square value of 586.309 and Sig. = .000, which is statistically significant, indicating that there is a significant variance between groups. Therefore, the Hotelling’s Trace test is appropriate due to its robustness in cases where there are differences in variance between groups.

Table 23. Multivariate Tests of Vastus lateralis morphologies difference

Test Name		Value	F	Hypothesis *df*	Error *df*	*p*
Hotelling’s Trace		.109	.200	6.000	11.000	.970
Tests of between-subjects effects						
Source	Dependent variable	Type III Sum of Square	*df*	Mean Square	F	Sig.
Group	MT $VL_{proximal}$	.246	1	.246	.600	.450
	MT VL_{middle}	.003	1	.003	.038	.847
	MT VL_{distal}	.063	1	.063	.533	.468
	MA $VL_{proximal}$	10038.336	1	10038.336	.421	.526
	MA VL_{middle}	.170	1	.170	1.044	.322
	MA VL_{distal}	722.500	1	722.500	0.230	.882
Error	MT $VL_{proximal}$	6.560	16	.410		
	MT VL_{middle}	1.827	16	.114		
	MT VL_{distal}	2.619	16	.163		
	MA $VL_{proximal}$	7662762.400	16	478922.650		
	MA VL_{middle}	3979601.375	16	248725.086		
	MA VL_{distal}	2231580.775	16	139473.798		

From the table 23, analyzing the variance of the Vastus lateralis morphologies, it was found that Hotelling’s Trace = .109, F = .200, Hypothesis *df* = 6.000, and *p* = .970, which was greater than the specified significance level (0.05). This indicated that there was no statistically significant difference in the effectiveness of the two training programs (TRAD and LLpBFR) in developing Vastus lateralis morphologies (p>.05).

4.5 Change in Vastus lateralis architecture

The following table displayed the pre-to-post changes in muscle fascicle angle, fascicle length and fascia thickness of vastus lateralis of the control group (TRAD) and the experimental group (LLpBFR).

4.5.1 Changes in Vastus lateralis fascicle angle, fascicle length and fascia thickness of vastus lateralis of the control group (TRAD)

Table 24. Changes in Vastus lateralis fascicle angle, fascicle length and fascia thickness

Sites	Pre x̄± S.D.	Post x̄± S.D.	□ (95% CI)	*t*	*df*	Sig(2-tailed)
Fascicle angle (degree)	15.55±5.03	17.34±2.90	1.79(-1.71;5.29)	1.158	9	.277
Fascicle length (mm)	71.98±10.76	84.11±7.92*	12.13(3.28;20.98)	3.100	9	.013
Fascia thickness (mm)	1.26±0.46	1.62±0.39	0.36(-.05;0.77)	1.964	9	.081
Data were reported as mean ± standard deviation.						

From table 24, Paired-sample t-test was conducted to compare pre-to-post changes in muscle fascicle angle, fascicle length and fascia thickness of vastus lateralis.

It was showed that at Pre (week 0), muscle fascicle angle, fascicle length and fascia thickness were 15.55±5.03degree, 71.98±10.76mm, and 1.26±0.46mm, respectively.

After finishing 6-week training of TRAD group, the results showed that muscle fascicle angle, fascicle length and fascia thickness increased up to 17.34±2.90degree, 84.11±7.92mm, and 1.62±0.39mm, respectively. Paired-sample t-test statistics demonstrated that only fascicle length significantly increased from baseline (□12.13, $CI_{95\%}$ = 3.28-20.98, t = 3.100, p = .013).

4.5.2 Changes in Vastus lateralis fascicle angle, fascicle length and fascia thickness of vastus lateralis of the experimental group (LLpBFR)

Table 25. Changes in Vastus lateralis fascicle angle, fascicle length and fascia thickness

Sites	Pre x̄± S.D.	Post x̄± S.D.	□ (95% CI)	*t*	*df*	Sig(2-tailed)
Fascicle angle (degree)	14.51±3.15	17.41±4.82	2.90(-.78;6.57)	1.863	7	.105
Fascicle length (mm)	74.01±10.31	85.83±7.28*	11.81(3.31;20.32)	3.284	7	.013
Fascia thickness (mm)	0.98±0.34	1.52±0.40*	0.55(.09;1.01)	2.827	7	.026
Data were reported as mean ± standard deviation.						

From table 25, Paired-sample t-test was conducted to compare pre-to-post changes in muscle fascicle angle, fascicle length and fascia thickness of vastus lateralis.

It was showed that at Pre (week 0), muscle fascicle angle, fascicle length and fascia thickness were 14.51±3.15degree, 74.01±10.31mm, and 0.98±0.34mm, respectively.

After finishing 6-week training of LLpBFR group, the results showed that muscle fascicle angle, fascicle length and fascia thickness increased up to 17.41±4.82degree, 85.83±7.28mm, and 1.52±0.40mm, respectively. Paired-sample t-test statistics demonstrated that fascicle length (□11.81, $CI_{95\%} = 3.31\text{-}20.32$, $t = 3.284$, $p = .013$) and fascia thickness (□0.55, $CI_{95\%} = 0.09\text{-}1.01$, $t = 2.827$, $p = .026$) significantly increased from baseline.

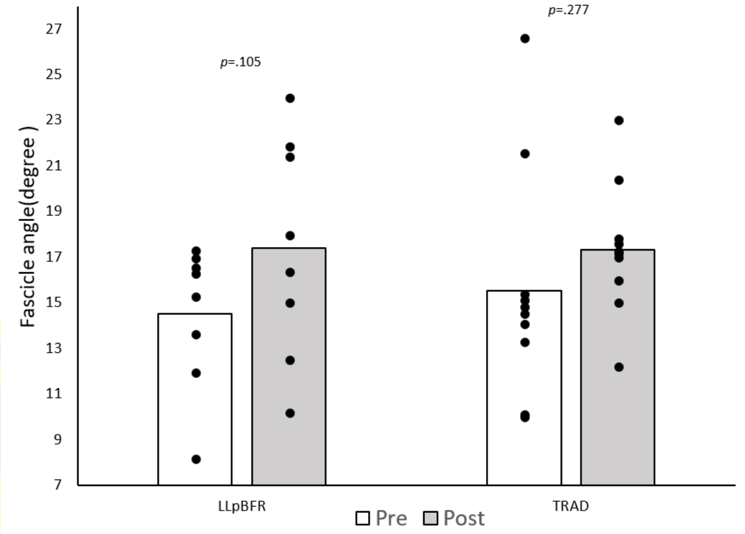


Figure 54. Fascicle angle at Pre and Post. * indicates p<.05 compared to Pre

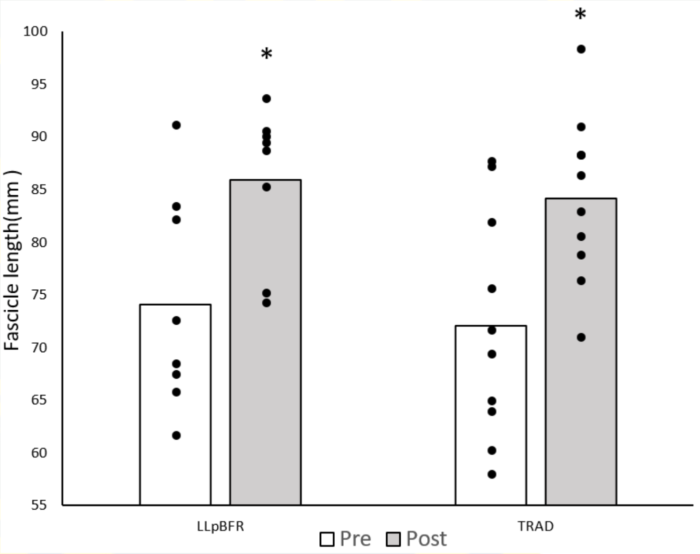


Figure 55. Fascicle length at Pre and Post. * indicates p<.05 compared to Pre

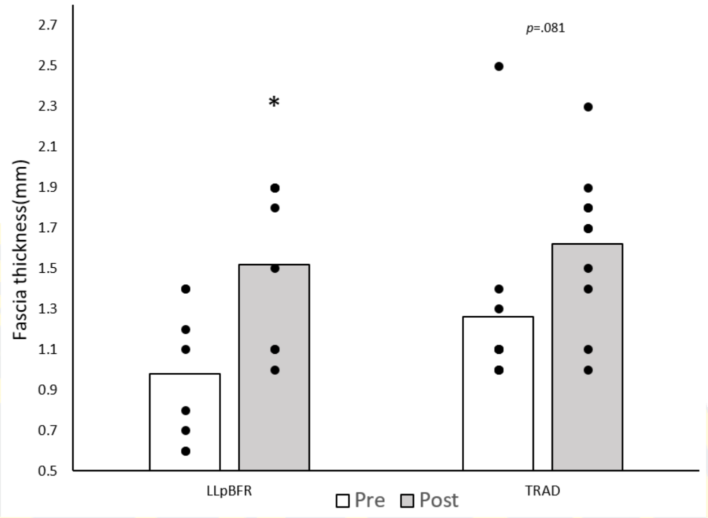


Figure 56. Fascia thickness at Pre and Post. * indicates p<.05 compared to Pre

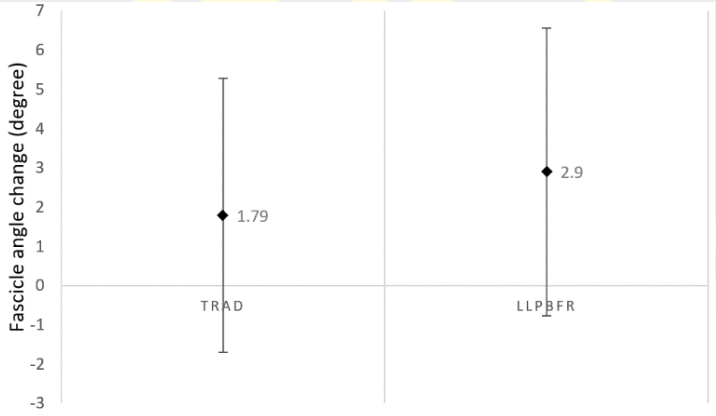


Figure 57. Change in Fascicle angle with 95%CI, * indicates p<.05 compare to Pre.

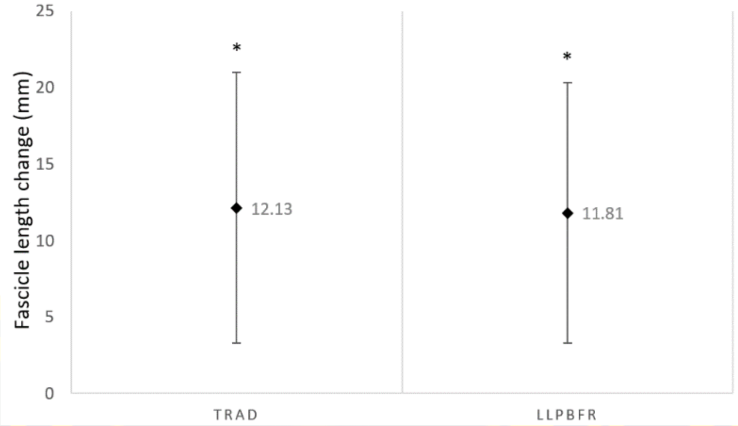


Figure 58. Change in Fascicle length with 95%CI, * indicates p<.05 compare to Pre.

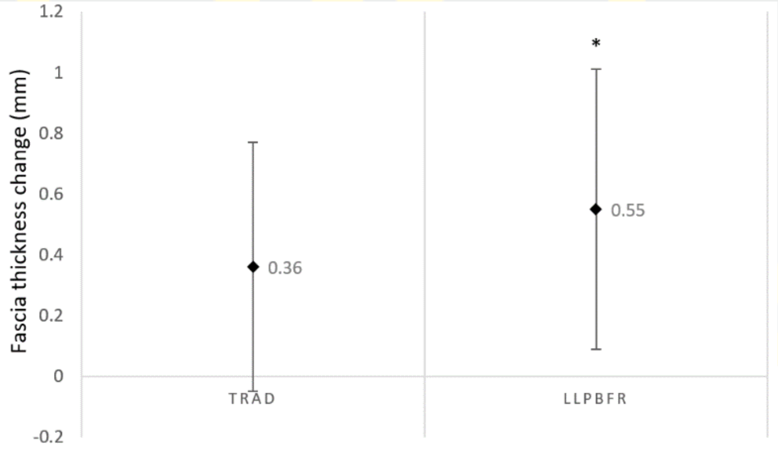


Figure 59. Change in Fascia thickness with 95%CI, * indicates p<.05 compare to Pre.

4.6 Vastus lateralis architecture difference

Table 26. Between-group comparison of Vastus lateralis architecture

	Group	$\bar{x}$	SD.	MANOVA
Fascicle angle (degree)	LLpBFR	17.41	4.82	Box's M = 7.507 F = .987 df1 = 6 df2 = 1582.708 Sig. = .432
	TRAD	17.34	2.90	
	Total	17.37	3.74	
Fascicle length (mm)	LLpBFR	85.83	7.28	
	TRAD	84.11	7.92	
	Total	84.87	7.47	
Fascia thickness (mm)	LLpBFR	1.52	0.40	Bartlet's Test of Sphericity Approx. Chi-Square = 77.604 df = 5 Sig. = .000
	TRAD	1.62	0.39	
	Total	1.58	0.38	

From table 26, Box's M statistic was calculated to verify the assumptions of multivariate analysis of variance (MANOVA).

The results from the Box's M test indicated that Box's M = 7.5707, F = .987, and Sig. = .432, which is higher than the significance level (*p*>.05). This suggests that the covariance matrices are not significantly different from each other, meeting the assumption for multiple analysis of variance.

The Bartlet's Test of Sphericity showed a Chi-square value of 77.604 and Sig. = .000, which is statistically significant, indicating that there is a significant variance between groups. Therefore, the Hotelling's Trace test is appropriate due to its robustness in cases where there are differences in variance between groups.

Table 27. Multivariate Tests of Vastus lateralis architecture difference

Test Name	Value	F	Hypothesis *df*	Error *df*	*p*
Hotelling's Trace	.042	.196	3.000	14.000	.897

Tests of between-subjects effects

Source	Dependent variable	Type III Sum of Square	df	Mean Square	F	Sig.
Group	Fascicle angle	.019	1	.019	.001	.972
	Fascicle length	13.072	1	13.072	.223	.643
	Fascia thickness	.040	1	.040	.260	.617
Error	Fascicle angle	237.997	16	14.875		
	Fascicle length	936.004	16	58.500		
	Fascia thickness	2.471	16	.154		

From the table 27, analyzing the variance of the Vastus lateralis architecture, it was found that Hotelling's Trace = .042, F = .196, Hypothesis *df* = 63.000, and *p* = .897, which was greater than the specified significance level (0.05). This indicated that there was no statistically significant difference in the effectiveness of the two training programs (TRAD and LLpBFR) in developing Vastus lateralis architecture morphologies (*p*>.05).

4.7 Change in isometric and dynamic strength

The following table displayed the pre-to-post changes in muscle isometric and dynamic strength of the control group (TRAD) and the experimental group (LLpBFR).

4.7.1 Changes in isometric and dynamic strength of the control group (TRAD)

Table 28. Changes in isometric and dynamic strength

	Pre x̄± S.D.	Post x̄± S.D.	□ (95% CI)	*t*	*df*	Sig(2-tailed)

Isometric elbow flexion (N)	43.90±12.55	62.80±5.47*	18.90(10.93;26.87)	5.365	9	.000
Isometric knee extension (N)	229.10±57.51	307.00±67.66*	77.90(55.88;99.92)	8.001	9	.000
1RM preacher curl (kg)	31.50±11.07	40.50±9.84*	9.00(6.73;11.26)	9.000	9	.000
1RM leg extension (lbs)	142.00±19.89	170.00±28.67*	28.00(17.99;38.00)	6.332	9	.000
Data were reported as mean ± standard deviation. Abbreviation; N=newtons; kg=kilograms; lbs=pounds; 1RM=1reptition maximum						

From table 28, Paired-sample t-test was conducted to compare pre-to-post changes of isometric and dynamic strength

It was showed that at Pre (week 0), isometric elbow flexor strength was 43.90±12.55N and dynamic elbow flexor strength was 31.50±11.07kg. Similarly, isometric knee extensor strength was 229.10±57.51N and dynamic knee extensor strength was 142.00±19.89kg.

After finishing 6-week training of TRAD group, the results showed that isometric elbow flexor strength increased to 62.80±5.47N (□18.90N, $CI_{95\%}$ = 10.93-26.97) and dynamic elbow flexor strength was 40.50±9.84kg (□9kg, $CI_{95\%}$ = 6.73-11.26). In the same way, isometric knee extensor strength increased to 307.00±67.66N (□77.90N, $CI_{95\%}$ = 55.88-99.92) and dynamic elbow flexor strength was 170.00±28.67kg (□28kg, $CI_{95\%}$ = 17.99-38.00). Paired-sample t-test statistics demonstrated that there were significant differences from pre-to-post change in all strength metrics (*p*=.000)

4.7.2 Changes in isometric and dynamic strength of the experimental group (LLpBFR)

Table 29. Changes in isometric and dynamic strength

	Pre x̄± S.D.	Post x̄± S.D.	□ (95% CI)	t	df	Sig(2-tailed)
Isometric elbow flexion (N)	48.63±10.29	67.38±13.24*	18.75(8.54;28.95)	4.344	7	.002
Isometric knee extension (N)	239.88±62.91	317.25±59.40*	77.37(43.32;111.43)	5.373	7	.004
1RM preacher curl (kg)	38.75±13.82	45.63±13.21*	6.88(3.04;10.70)	4.245	7	.001
1RM leg extension (lbs)	153.75±39.98	195.00±59.52*	41.25(20.08;62.42)	4.608	7	.003

Data were reported as mean ± standard deviation. Abbreviation; N=newtons; kg=kilograms; lbs=pounds; 1RM=1reptition maximum

From table 29, Paired-sample t-test was conducted to compare pre-to-post changes of isometric and dynamic strength

It was showed that at Pre (week 0), isometric elbow flexor strength was 48.63±10.29N and dynamic elbow flexor strength was 38.75±13.82kg. Similarly, isometric knee extensor strength was 239.88±62.91N and dynamic knee extensor strength was 153.75±39.98kg.

After finishing 6-week training of LLpBFR group, the results showed that isometric elbow flexor strength increased to 67.38±13.24N (□18.75N, $CI_{95\%}$ = 8.54-28.95) and dynamic elbow flexor strength was 45.63±13.21kg (□6.88kg, $CI_{95\%}$ = 3.04-10.70). In the same way, isometric knee extensor strength increased to 317.25±59.40N (□77.90N, $CI_{95\%}$ = 43.32-111.43) and dynamic elbow flexor strength was 195.00±59.52kg (□28kg, $CI_{95\%}$ = 20.08-62.42). Paired-sample t-test statistics demonstrated that there were significant differences from pre-to-post change in all strength metrics (*p*<.05).

4.8 Change in ankle-brachial index

The following table displayed the pre-to-post changes in ankle-brachial index of the control group (TRAD) and the experimental group (LLpBFR).

Table 30. Change in Ankle Brachial Index

Group	Pre x̄± S.D.	Post x̄± S.D.	□ (95% CI)	*t*	*df*	Sig(2-tailed)
TRAD (A.U.)	1.09±0.10	1.08±0.09	-0.02(-0.11;0.06)	-.612	9	.555
LLpBFR (A.U.)	1.17±0.15	1.12±0.11	-0.05(-0.20;0.11)	-.743	7	.482
Data were reported as mean ± standard deviation. Abbreviation; A.U.=arbitrary unit						

Table 30 showed that Paired-sample t-test was conducted to compare pre-to-post changes of ABI.

It was showed that at Pre (week 0), ABI were 1.09±0.10 and 1.17±0.15 in TRAD and LLpBFR, respectively. After finishing 6-week training, the results showed that ABI were 1.08±0.09 (□-0.02, $CI_{95\%}$ = -0.11-0.06) and 1.12±0.11 (□-0.05, $CI_{95\%}$ = -0.20-0.11), in TRAD and LLpBFR, respectively. Paired-sample t-test statistics demonstrated that there was no significant difference from pre-to-post change in ABI in both groups (*p*>.05).

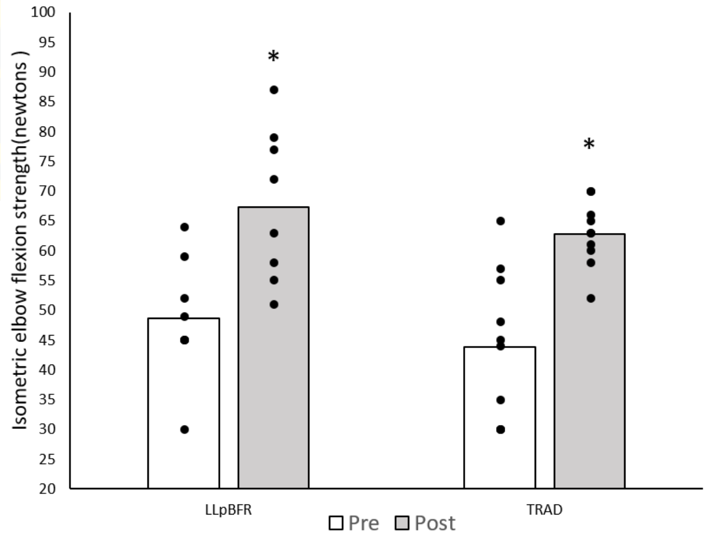


Figure 60. Isometric elbow flexion strength at Pre to Post. * indicates p<.05 compared to Pre

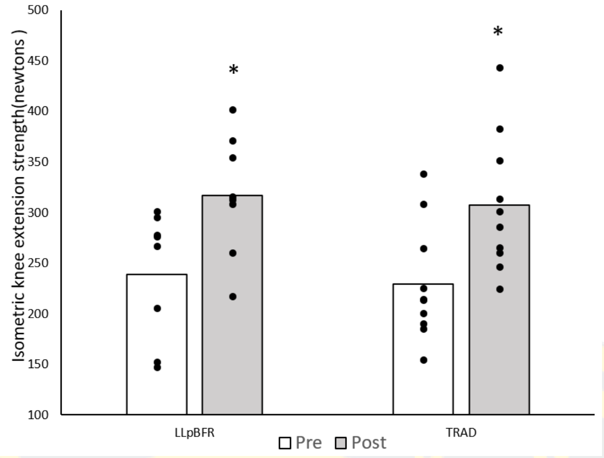


Figure 61. Isometric knee extension strength at Pre to Post. * indicates p<.05 compared to Pre

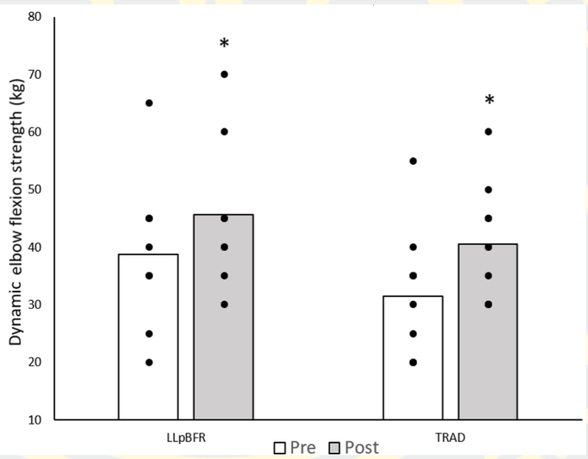


Figure *62*. Dynamic elbow flexion strength at Pre to Post. * indicates p<.05 compared to Pre

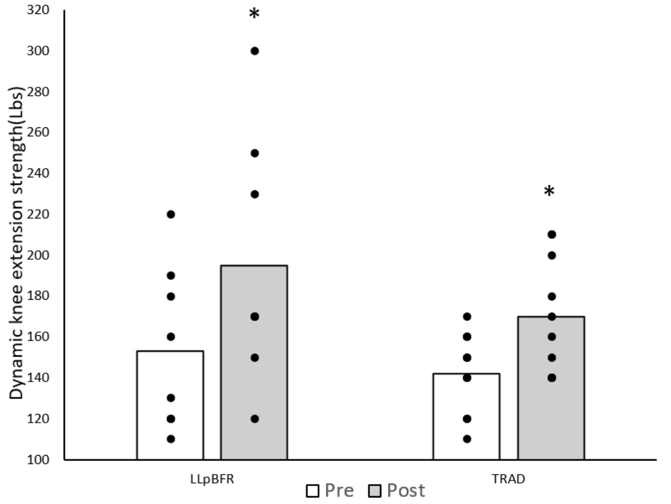


Figure 63. Dynamic knee extension strength at Pre to Post. * indicates p<.05 compared to Pre

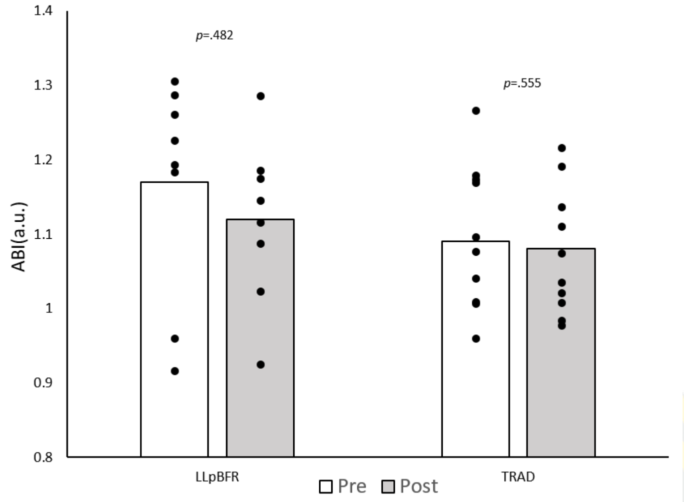


Figure 64. Ankle-brachial index at Pre to Post. * indicates p<.05 compared to Pre

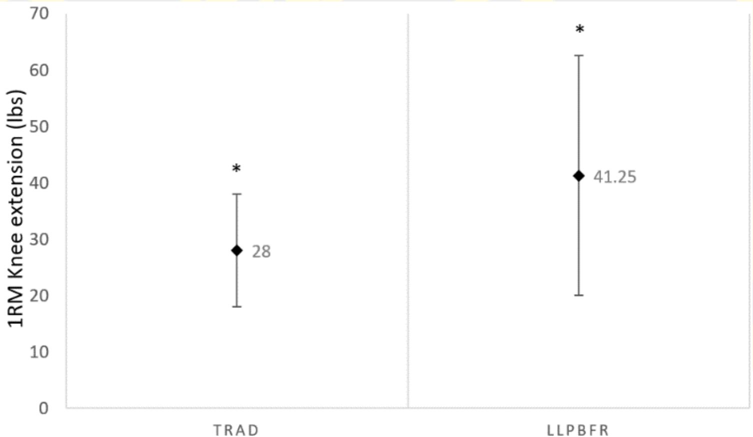


Figure 65. Change in 1RM Knee extension with 95%CI, * indicates p<.05 compare to Pre.

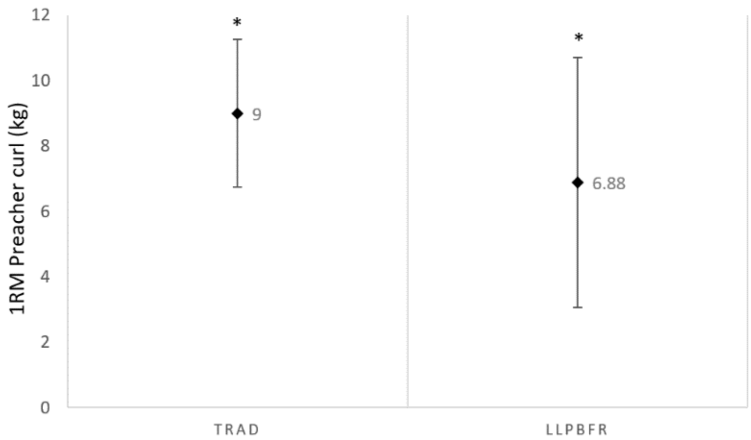


Figure 66. Change in 1RM Preacher curl with 95%CI, * indicates p<.05 compare to Pre.

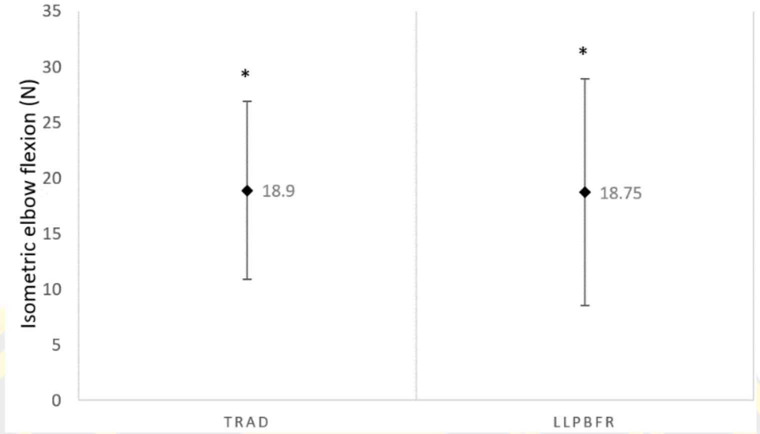


Figure 67. Change in Isometric elbow flexion with 95%CI, * indicates p<.05 compare to Pre.

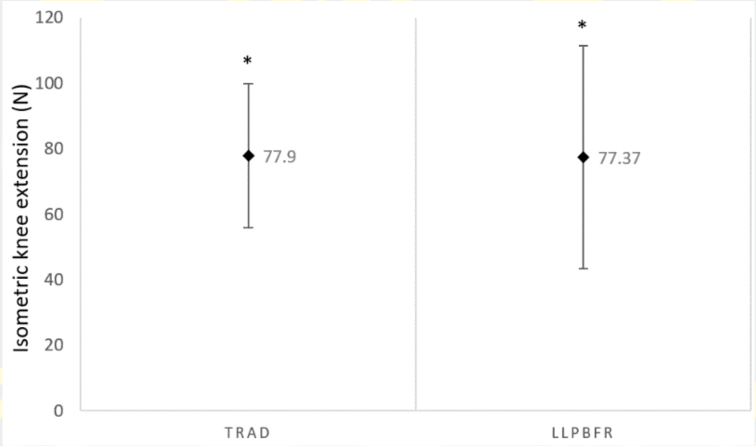


Figure 68. Change in Isometric knee extension with 95%CI, * indicates p<.05 compare to Pre.

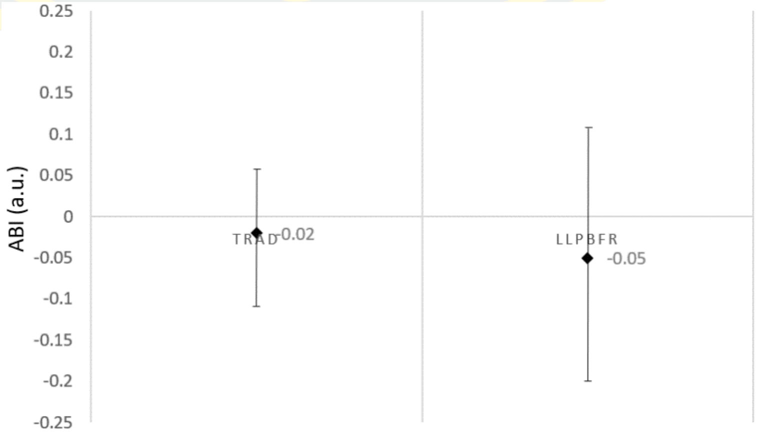


Figure 69. Change in ABI with 95%CI. * indicates p<.05 compare to Pre.

4.9 Change in isometric strength: body weight ratio

The following table displayed the pre-to-post changes in isometric strength: body weight ratio of the control group (TRAD) and the experimental group (LLpBFR).

4.9.1 Changes in isometric strength: body weight ratio of the control group (TRAD)

Table *31*. Changes in isometric strength: body weight ratio

	Pre x̄± S.D.	Post x̄± S.D.	□ (95% CI)	*t*	*df*	Sig(2-tailed)
Elbow flexion strength: body weight ratio (N/kg)	0.65±0.21	0.94±0.17*	0.28(0.14;0.42)	4.713	9	.001
Knee extension strength: body weight ratio (N/kg)	3.39±0.90	4.50±0.93*	1.11(0.87;1.36)	10.240	9	.000
Data were reported as mean ± standard deviation. Abbreviation; N/kg = Newton/kilograms						

From table 31, Paired-sample t-test was conducted to compare pre-to-post changes of isometric and dynamic strength

It was showed that at Pre (week 0), isometric elbow flexor strength was 43.90±12.55N and dynamic elbow flexor strength was 31.50±11.07kg. Similarly, isometric knee extensor strength was 229.10±57.51N and dynamic knee extensor strength was 142.00±19.89kg.

After finishing 6-week training of TRAD group, the results showed that isometric elbow flexor strength increased to 62.80±5.47N (□18.90N, $CI_{95\%}$ = 10.93-26.97) and dynamic elbow flexor strength was 40.50±9.84kg (□9kg, $CI_{95\%}$ = 6.73-11.26). In the same way, isometric knee extensor strength increased to 307.00±67.66N (□77.90N, $CI_{95\%}$ = 55.88-99.92) and dynamic elbow flexor strength was 170.00±28.67kg

(□28kg, $CI_{95\%}$ = 17.99-38.00). Paired-sample t-test statistics demonstrated that there were significant differences from pre-to-post change in all strength metrics (*p*=.000).

4.9.2 Changes in isometric strength: body weight ratio of the experimental group (LLpBFR)

Table 32. Changes in isometric strength: body weight ratio

	Pre x̄± S.D.	Post x̄± S.D.	□ (95% CI)	t	df	Sig(2-tailed)
Elbow flexion strength: body weight ratio (N/kg)	0.73±0.21	1.00±0.17*	0.27(0.14;0.39)	5.052	7	.001
Knee extension strength: body weight ratio (N/kg)	3.57±1.02	4.70±1.00*	1.13(0.68;1.59)	5.849	7	.001

Data were reported as mean ± standard deviation. Abbreviation; N/kg = Newton/kilograms

From table 32, Paired-sample t-test was conducted to compare pre-to-post changes of isometric and dynamic strength

It was showed that at Pre (week 0), isometric elbow flexor strength was 48.63±10.29N and dynamic elbow flexor strength was 38.75±13.82kg. Similarly, isometric knee extensor strength was 239.88±62.91N and dynamic knee extensor strength was 153.75±39.98kg.

After finishing 6-week training of LLpBFR group, the results showed that isometric elbow flexor strength increased to 67.38±13.24N (□18.75N, $CI_{95\%}$ = 8.54-28.95) and dynamic elbow flexor strength was 45.63±13.21kg (□6.88kg, $CI_{95\%}$ = 3.04-10.70). In the same way, isometric knee extensor strength increased to 317.25±59.40N (□77.90N, $CI_{95\%}$ = 43.32-111.43) and dynamic elbow flexor strength was 195.00±59.52kg (□28kg, CI95% = 20.08-62.42). Paired-sample t-test statistics demonstrated that there were significant differences from pre-to-post change in all strength metrics (p<.05).

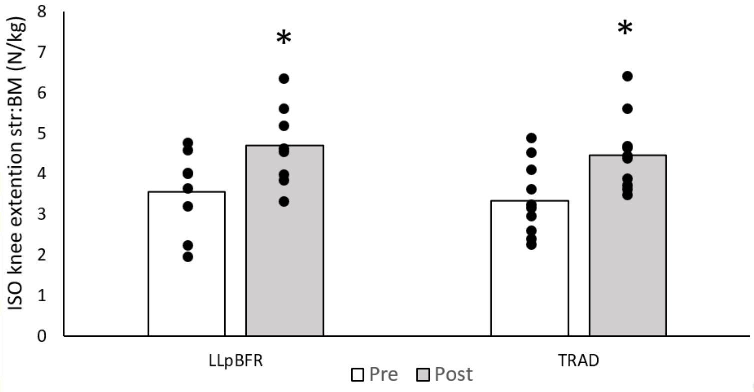


Figure 70. Isometric knee extension strength: body weight ratio at Pre to Post. * indicates p<.05 compared to Pre

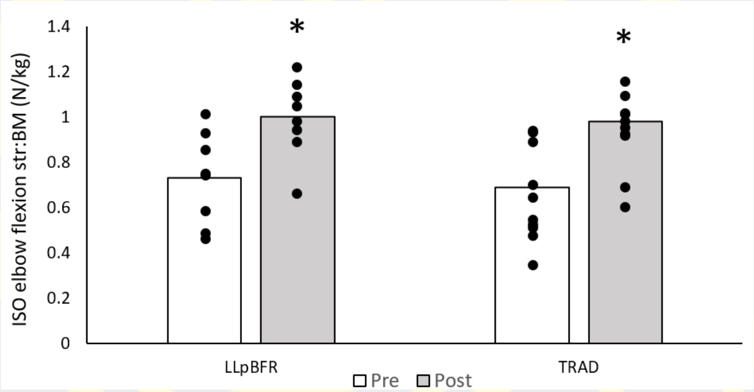


Figure 71. Isometric elbow flexion strength: body weight ratio at Pre to Post. * indicates p<.05 compared to Pre

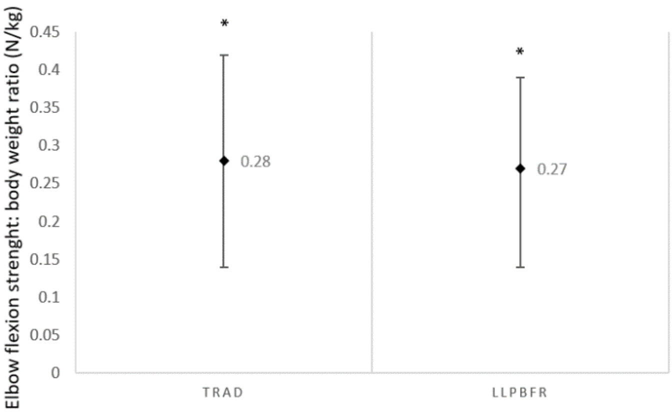


Figure 72. Change in isometric elbow flexion strength: body weight ratio with 95%CI, * indicates p<.05 compare to Pre.

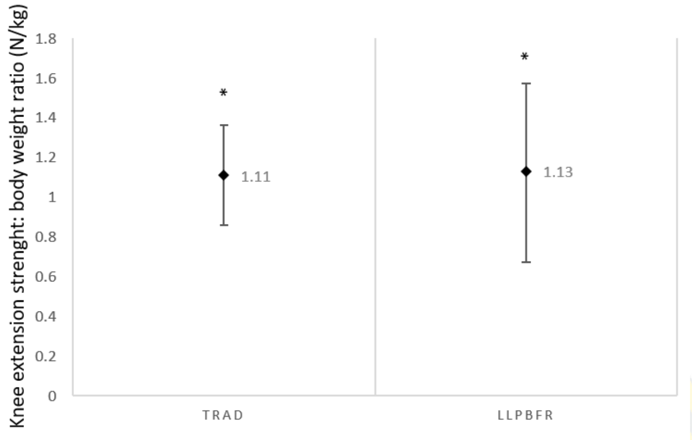


Figure 73. Change in isometric knee extension strength: body weight ratio with 95% CI, * indicates p<.05 compare to Pre.

4.10 Physiologies difference

Table 33. Between-group comparison of physiologies

	Group	x̄	SD.	MANOVA
Isometric elbow flexion (N)	LLpBFR TRAD Total	67.38 62.80 64.83	13.24 5.47 9.67	
Isometric knee extension (N)	LLpBFR TRAD Total	317.25 307.00 311.56	59.40 67.66 62.48	Box's M = 130.160 F = 2.295 df1 = 28 df2 = 787.885 Sig. = .000
1RM preacher curl (kg)	LLpBFR TRAD Total	45.63 40.50 42.78	13.21 9.85 11.40	
1RM leg extension (lbs)	LLpBFR TRAD Total	195.00 170.00 181.11	59.52 28.67 45.36	Bartlet's Test of Sphericity Approx. Chi-Square = 462.836 df = 27 Sig. = .000
Elbow flexion strength: body weight ratio (N/kg)	LLpBFR TRAD Total	1.00 0.94 0.96	0.17 0.17 0.17	
Knee extension strength: body weight ratio (N/kg)	LLpBFR TRAD Total	4.70 4.50 4.59	1.00 0.93 0.93	
ABI (A.U.)	LLpBFR TRAD Total	1.12 1.08 1.09	0.11 0.09 0.10	

From table 33, Box's M statistic was calculated to verify the assumptions of multivariate analysis of variance (MANOVA).

The results from the Box's M test indicated that Box's M = 130.160, F = 2.295, and Sig. = .000, which is less than the significance level (p<.05). This suggests that the covariance matrices are significantly different from each other, indicating a violation of the assumption of homogeneity of covariance matrices.

The Bartlet's Test of Sphericity showed a Chi-square value of 462.836 and Sig. = .000, which is statistically significant, indicating that there is a significant variance between groups. From all these, the Pillai's Trace test is appropriate due to its robustness to violations of the assumptions of homogeneity of covariance matrices.

Table 34. Multivariate Tests of physiologies difference

Test Name		Value	F	Hypothesis *df*	Error *df*	*p*
Pillai's Trace		.245	.463	7.000	10.00	.841
Tests of between-subject's effects						
Source	Dependent variable	Type III Sum of Square	df	Mean Square	F	Sig.
Group	Isometric elbow flexion	93.592	1	93.025	.994	.335
	Isometric knee extension	466.944	1	466.944	.113	.741
	1RM preacher curl	116.736	1	116.736	.892	.359
	1RM leg extension	2777.778	1	2777.778	1.380	.257
	Elbow flexion strength: body weight ratio	.017	1	.017	.589	.545
	Knee extension strength: body weight ratio	.172	1	.172	.188	.671
	Ankle brachial index	.009	1	.009	.877	.363
Error	Isometric elbow flexion	1497.475	16	93.592		
	Isometric knee extension	65895.500	16	4118.469		
	1RM preacher curl	2094.375	16	130.898		

	1RM leg extension	32200.000	16	2012.500
	Elbow flexion strength: body weight ratio	.471	16	.029
	Knee extension strength: body weight ratio	14.674	16	.917
	Ankle brachial index	.155	16	.010

From the table 34, analyzing the variance of the physiologies difference, it was found that Pillai's Trace = .245, F = .463, Hypothesis *df* = 7.000, and *p* = .841, which was greater than the specified significance level (0.05). This indicated that there was no statistically significant between two training programs (TRAD and LLpBFR) on physiological adaptation (*p*>.05).

4.11 Rate of perceived exertion difference

Table 35. Between-group comparison of rate of perceived exertion

	Group	x̄	SD.	MANOVA
OMNI-RES Week 1	LLpBFR	6.75	0.89	
	TRAD	7.80	0.63	
	Total	7.33	0.91	
OMNI-RES Week 2	LLpBFR	6.88	0.64	
	TRAD	8.20	0.63	Box's M = 38.334 F = 1.039 df1 = 21 df2 = 830.320 Sig. = .413
	Total	7.61	0.92	
OMNI-RES Week 3	LLpBFR	8.50	0.76	
	TRAD	8.40	0.70	
	Total	8.44	0.70	
OMNI-RES Week 4	LLpBFR	8.13	0.99	Bartlet's Test of Sphericity Approx. Chi-Square = 15.976 df = 20 Sig. = .727
	TRAD	8.40	0.52	
	Total	8.28	0.75	
OMNI-RES Week 5	LLpBFR	9.00	0.76	
	TRAD	8.40	0.70	
	Total	8.67	0.77	
OMNI-RES Week 6	LLpBFR	8.63	0.52	
	TRAD	8.50	0.53	
	Total	8.56	0.51	

From table 35, Box's M statistic was calculated to verify the assumptions of multivariate analysis of variance (MANOVA).

The results from the Box's M test indicated that Box's M = 38.334, F = 1.039, and Sig. = .413, which is higher than the significance level (*p*>.05). This suggests that the covariance matrices are not significantly different from each other, meeting the assumption for multiple analysis of variance.

The Bartlet's Test of Sphericity showed a Chi-square value of 15.975 and Sig. = .727, which is not statistically significant, indicating that there is not a significant variance between groups. In this case, the Wilks' Lambda is appropriate because it assesses the overall significance of group differences under the assumption of equal covariance matrices.

Table *36*. Multivariate Tests of rate of perceived exertion difference

Test Name	Value	F	Hypothesis *df*	Error *df*	*p*
Wilks' Lambda	.300	4.281	6.000	11.00	.018

Tests of between-subjects effects

Source	Dependent variable	Type III Sum of Square	df	Mean Square	F	Sig.
Group	OMNI-RES Week1	4.900	1	4.900	8.615	.010
	OMNI-RES Week2	7.803	1	7.803	19.281	.000
	OMNI-RES Week3	.044	1	.044	.085	.775
	OMNI-RES Week4	.336	1	.336	.580	.457
	OMNI-RES Week5	1.600	1	1.600	3.048	.100
	OMNI-RES Week6	.069	1	.069	.254	.621
Error	OMNI-RES Week1	9.100	16	.596		
	OMNI-RES Week2	6.475	16	.405		
	OMNI-RES Week3	8.400	16	.525		
	OMNI-RES Week4	9.275	16	.580		
	OMNI-RES Week5	8.400	16	.525		

	OMNI-RES Week6	4.375	16	.273	

From the table 36, analyzing the variance of the rate of perceived exertion difference, it was found that Wilks' Lambda = .300, F = 4.281, Hypothesis *df* = 6.000, and *p* = .018, which was lower than the specified significance level (0.05). This indicated that there was statistically significant between two training programs (TRAD and LLpBFR) on OMNI-RES (p>.05).

Tests of between-subjects effects analysis showed that there was the main group effect at week 1 ($F_{[1,16]}$ = 8.615, p =.010, η^{p}_{2} = .350) and week 2 ($F_{[1,16]}$ = 19.281, p =.000, η^{p}_{2} = .546), indicating that the two training programs had significantly different impacts on OMNI-RES. This means that participants in the TRAD and LLpBFR groups reported significantly different perceived exertion levels in week 1 and 2, with the effect size *Large* at both time points.

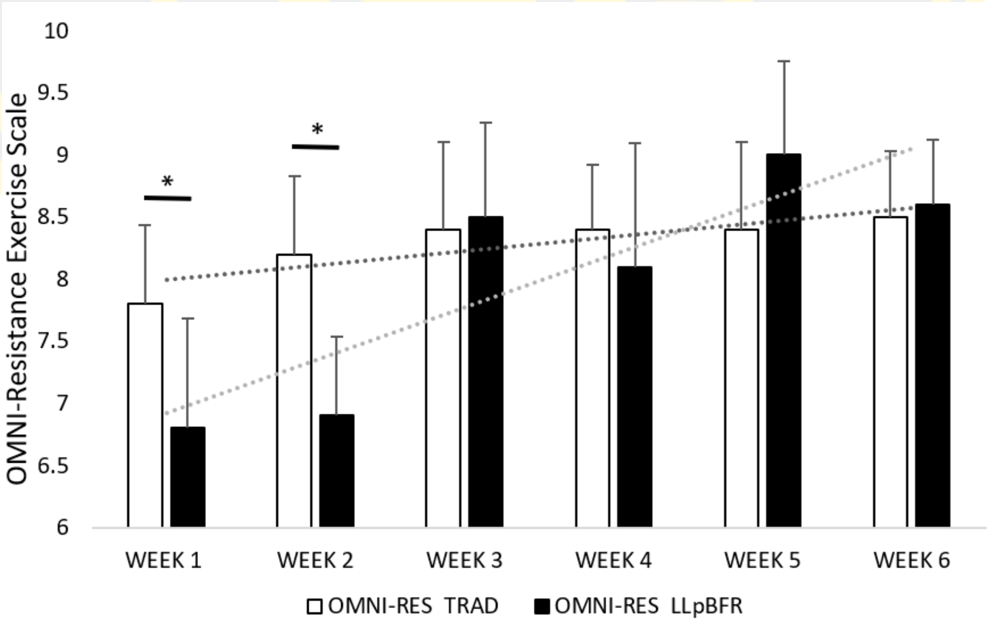


Figure 74. OMNI-RES scores from week 1-6. * indicates p<.05 significant different between groups.

CHAPTER 5

DISCUSSION

In this chapter, the findings of this study were discussed and compared to previous research. Additionally, potential mechanisms for these findings were analyzed and presented where logical reasoning supported them. The discussion would be separated into 6 parts:

1. **Muscle cross-sectional area and muscle thickness of Biceps brachii**
2. **Muscle cross-sectional area and muscle thickness of Vastus lateralis**
3. **Vastus lateralis architecture**
4. **Muscle strength**
5. **Ankle-Brachial Index**
6. **Rate of perceived exertion**

1. Muscle cross-sectional area and muscle thickness of Biceps brachii

The main findings of this study were both TRAD and LLpBFR significantly increased muscle cross-sectional area, as measured via MRI, at proximal (□63.80mm^2 and □65.25mm^2 ,respectively), middle (□41.20mm^2 and □56.25mm^2, respectively), and distal (□102.40mm^2 and □135.00mm^2, respectively) regions and muscle thickness, as measured via US, at middle (□0.45cm and □0.47cm, respectively) and distal (□0.47cm and □0.42cm, respectively) regions (all $p<.05$), with no significant different when comparing between-group effect ($p=.818$). However, muscle thickness at proximal region did not significantly increase in both groups ($p>.05$).

It was worth noting that the percentage increases in muscle size were non-uniform, supporting the evidence of regional hypertrophy where muscle size did not equally increase throughout the muscle belly after training (Nunes et al., 2024). In a previous study, Wakahara et al. (2013) investigated the effect of 12-week elbow extensors training using the lying dumbbell press exercise and T2-MRI to determine the activated areas of the triceps brachii. The results demonstrated that the area of triceps brachii that was activated the most was at the middle region (10 cm away from the distal region), with this region showing greater activation than the proximal region (28 cm away from the distal region). Furthermore, after 12 weeks of training, MRI scans revealed that the relative percent increase in muscle cross-sectional area was highest at the middle region (about 23% increase), which corresponded perfectly with the triceps brachii area most activated during the dumbbell press exercise. In contrast, the muscle cross-sectional area at the proximal region, which was the least activated, only increased by about 10% (Wakahara et al., 2013).

This supported the relationship between muscle activation and muscle hypertrophy. Vigotsky et al. (2022) demonstrated the logical basis that muscle activation could potentially be related to muscle hypertrophy and that we could measure muscle activation using the electromyography technique (EMG). They suggested that the neuromuscular excitation, starting in the brain and sending the signal to the muscle to activate, inducing the repeated crossbridge attachments of actin-myosin filaments, could be related to muscle growth because the muscle that would hypertrophy must be the muscle that was working (Vigotsky et al., 2022). Therefore, the premise was that if the EMG signal was high, it was supposed that the muscle was working to a great extent, causing mechanical tension in the muscle, which ultimately leads to muscle hypertrophy (Schoenfeld, 2010).

Although this current study did not investigate the muscle activation, the previous study conducted by Oliveira et al. (2013), providing the interesting insight about this. Oliveira and team recruit a group of healthy male subjects to their study and investigated the muscle activation using EMG of preacher curl exercise. They found that preacher curl exercise induced the highest levels of muscle activation, particularly at the onset of the concentric phase (also straight elbow flexion). Additionally, muscle activation during the latter stages of the eccentric or lowering phase was also significantly elevated. This suggested that the biceps brachii muscle was maximally engaged when fully stretched and when starting to shortened from straight elbow position. These force-time characteristics might potentially contribute to regional distal hypertrophy because there was the existing evidence that when muscle was stretched to its maximal extent and activated, there was the phenomenon known as stretched-mediated hypertrophy occurring (Warneke et al. 2023).

Stretch-mediated hypertrophy was the physiological phenomenon by which muscle growth was induced through the mechanical stretch of myofilaments (Warneke et al. 2022). This type of hypertrophy occurred when muscles were subjected to a prolonged stretch, which led to the activation of various signaling pathways such as mTOR and growth factors that promoted muscle protein synthesis and cell growth (Vissing et al. 2013). The mechanical stretch caused changes in the muscle's internal environment, including an increase in internal tension and cellular deformation, which subsequently leading to the addition of more sarcomere in series (Yahata et al. 2021). This process highlighted the importance of stretching exercises and their potential role in enhancing muscle size and strength as showed by the recent study that maximal stretching training of the plantar flexors could potentially cause surprisingly substantial hypertrophic results, about 4-8% increases in muscle thickness as measured via US technique (Warneke et al. 2023). In the research setting, measuring the increase of additional sarcomeres in series was usually performed by US technique and looking at muscle fascicle length whether or not it was significantly increase. In this current study, we found the supported by the current findings demonstrated that in our vastus lateralis muscle which was trained by knee extension machine, full range of motion as well, there were the significantly increases of fascicle length in both TRAD and LLpBFR group (□16.85% and □15.97%, respectively, all $p<.05$)

Moreover, the evidence supporting training at full stretch was conducted by Pinto et al. (2012). They compared preacher curl exercise at different range of motion and muscle hypertrophy. They recruited 40 healthy young men with no resistance training experience to the study and randomly assigned to either training preacher curl at full range of motion (elbow extended straight to 130^o elbow flexion) or training in limited short range of motion (50^o to 100^o elbow flexion). After 10-week program, muscle thickness was measured via US technique at 60% of humerus length, corresponding to the middle region of this study, they found that the group training with full range of motion significantly increased biceps brachii thickness up 9.52% compared the partial range of motion, 7.37% (Pinto et al. 2012). The higher extent of hypertrophy might partially attribute training at longer range of motion that involved more muscle stretch in full range of motion group.

Moreover, as supported by this current study as well, the finding of this study demonstrated that both the percent increases in muscle cross-sectional area and muscle thickness were obviously higher in the distal region than the proximal region in both training protocols. Specifically, the results demonstrated that the relative percent increases in muscle cross-sectional area at distal region in TRAD group was 12.15% and in LLpBFR group was 16.92% compared to proximal regions which were about 8.26% and 9.02% in TRAD and LLpBFR, respectively. Moreover, muscle thickness reinforced this finding, demonstrated that the percent increases in muscle thickness at distal regions were 25.27% in TRAD and 21.76% in LLpBFR compared to the proximal regions which were only 5.07% and 6.36% in TRAD and LLpBFR, respectively.

The finding of preacher curl exercise that preferentially biased muscle hypertrophy at distal region was supported by previous studies. For instance, Zabaleta-Korta et al. (2023) investigated hypertrophic effects of inclined dumbbell curl exercise and preacher exercise on regional muscle growth. 38 healthy women were recruited to the study and randomly assigned to either inclined dumbbell curl exercise group or preacher curl exercise group. The intensity of training in Zabaleta-Korta's study was similar to our current TRAD group which was set at about 12RM or 70%1RM. Besides, muscle hypertrophy measurement methodology via the increases in muscle thickness of biceps brachii at 50%, 60%, and 70% regions of humerus length was also similar to this study. After 9 weeks of training, 12 sets per week, they found that the significant increase from pre intervention was observed at only distal region of biceps brachii thickness in preacher curl exercise group (□9.7% or □0.26cm increase from baseline). Although the thickness of biceps brachii at proximal and middle regions also increased from preacher curl training, statistical significance was not reached (□6.57% or 0.14cm at proximal region and □7.76% or 0.18cm at middle region, all $p>.05$).

It was worth mentioning when comparing Zabaleta-Korta's finding to this current study, the training status of our participants were different. Zabaleta-Korta's employed resistance trained female participants while this current study recruited "untrained" male participants. Therefore, there were two caveats to note at this point. Firstly, untrained participants usually experienced the phenomenon known as novice gain, which made them hyperresponsive to muscle hypertrophy to very huge extent (Vissing et al. 2008). This was also supported by the recent meta-analysis by Arntz et al. (2022), demonstrating that when comparing between athlete and non-athlete participants, the non-athlete group showed the greater extent of muscle hypertrophy after period of training regardless of the age. This might explain why the gain in muscle thickness at distal region of this current study, regardless of the training condition, was superior comparing to previous finding (e.g. distal hypertrophy: 0.47cm in TRAD and 0.42cm in LLpBFR vs 0.26cm in Zabaleta-Korta's). Secondly, biological difference might have partial effect on muscle hypertrophic extent. For example, Kosek et al. (2006) compared hypertrophic response between males and females, age 26-27 years, and found that after 16 weeks of quadriceps training program, muscle cross-sectional areas of type I fiber increased □8% and □15% in females and males, respectively. Moreover, the percentage differences were more obvious in type IIa and IIb fiber cross-sectional areas after training (□18% and □27%, respectively in females and □28% and □34%, respectively in males). Therefore, male participants in this current study might as well experience higher extent of muscle hypertrophy compared to female participants in Zabaleta-Korta's.

Moreover, when comparing between Zabaleta-Korta's study and this current study with group of similar training intensity, the TRAD increased biceps brachii thickness the proximal region at 0.11cm which was very close to the finding of Zabaleta-Korta's (0.14cm). The LLpBFR group also supported this finding with only 0.13cm increase in biceps brachii thickness at proximal region. However, the increase in middle region of this current study was in contrast with Zabaleta-Korta's reports (2023). At the middle region, this current study demonstrated the significant increases of biceps brachii thickness at 0.45cm (*p*=.003) and 0.47cm (*p*=.001) from TRAD and LLpBFR groups, respectively. Collectively, this current study and Zabaleta-Korta's study suggested that preacher curl exercise was not much effective in inducing muscle hypertrophy at proximal region, despite of different resistance training protocols, and preacher curl exercise was very effective to induce muscle hypertrophy at distal region of biceps brachii. Nevertheless, the effectiveness in inducing middle region hypertrophy was still conflicting.

The finding was also supported by another study conducted by Pedrosa et al. (2023). They compared the two different protocols of preacher curl exercise but with dumbbell. 19 young healthy women participants in this study. One group was assigned to performing preacher curl at initial range of motion from elbow flexion 0^o (straight arm) to 68^o and another group was performing at final range of motion from 68^o to 130^o of elbow flexion. Muscle cross-sectional area of biceps brachii was measured via US technique at 50% (proximal region) and 70% (distal region) of muscle length. The results demonstrated that when performing preacher curl exercise at the initial range of motion, muscle cross-sectional area significantly increased at distal region (95%CI = 0.18cm^2 to 0.59 cm^2, *p*=.001, ES=0.89). Moreover, they also supported by showing statistically analysis that proximal region was not significantly different from baseline after training (95%CI = -0.10cm^2 to 0.34 cm^2, *p*=.331, ES=0.23). In our current study, the participants performed full range of motion in every repetition, therefore, they must also perform initial range of motion as well and this might explain the similar findings in increase in muscle hypertrophy at distal region.

However, this current study provided a more comprehensive analysis by addressing hypertrophy in the middle region of the muscle, which was overlooked be Pedrosa and colleague's study. They only compared the regional cross-sectional area of the biceps brachii at 50% (proximal region) and 70% (distal region), by them assessing muscle hypertrophic metrics, neglecting the middle region. This omission limited the deeper understanding of specific regional hypertrophy. Anyway, this current study filled this gap. While our findings supported Pedrosa et al. (2023) in showing greater growth in the distal region compared to the proximal region following preacher curl exercises, our outcome data also demonstrated that both TRAD and LLpBFR resulted in higher relative percent increases in muscle thickness in the middle region compared to the proximal region (22.96% vs. 5.07% in TRAD and 24.48% vs. 6.36% in LLpBFR).

Additionally, the ineffectiveness of preacher curl exercise in eliciting proximal hypertrophy was confirmed by a study conducted by Nunes et al. (2020). This time the researchers recruited 35 participants both male and female to their study. One group was assigned to preacher curl exercise with free-weight barbell and the other group was assigned to preacher curl exercise with cable-pulley system. The logical basis behind these was that the highest torque application on biceps brachii would be when muscle was shortened from using cable-pulley system while the highest torque application, in contrast, would be when muscle was fully lengthened from free-weight barbell. Muscle hypertrophic response was measured by using US to measure muscle thickness at 50% region, corresponding to the proximal region of this current study. The findings demonstrated that after 10 weeks of training, at intensity around 8-12RM of 9 sets per week, despite of different torque applications on biceps brachii and equipment, muscle thickness revealed similar pattern of increases. The findings demonstrated that participants only experience just little increases, □2mm or 7-8% (ES=*Small*) from baseline (Nunes et al. 2020). Interestingly, our own findings echoed these findings, revealing a 1.1mm increase in TRAD and a 1.3mm increases in LLpBFR. It's worth noting that Nunes' study likely achieved a little higher percentage of hypertrophy due to its longer training duration (10 vs 6 weeks, respectively) and more frequency (3 vs 1 session, respectively) compared to this study.

For practical application about program design, the findings of this study supported the thought process of hypertrophy program design, that practitioners aiming to maximize muscle growth across all regions of a muscle should incorporate multiple exercises targeting the muscle (Baz-Valle et al., 2019). Our results revealed that exclusively performing preacher curls could not fully optimize the size of the proximal region of the biceps brachii. This logical basis was supported by the previous study of Costa et al. (2021). They similarly demonstrated that incorporating a variety of exercises, such as standard biceps curls, preacher curls, and inclined dumbbell curls, across training sessions resulted in superior absolute increases in the percentage of muscle regional hypertrophy across proximal, middle, and distal regions (Costa et al. 2021). This was further reinforced by previous studies which showed that engaging in various exercises targeting a specific muscle led to different patterns of muscle activation, potentially contributing to hypertrophy across various regions of the muscle (Finni et al. 2008; Wakahara et al. 2013). Furthermore, another work by Zabaleta-Korta et al. (2021) demonstrated about the role of various exercises, such as smith machine squats and leg extensions, leading to distinct regional hypertrophy in the legs. Their findings showed that even with identical volume and intensity protocols, squats and leg extensions produced different patterns of muscle growth. Specifically, squats led to more significant increases in the vastus lateralis, while leg extensions primarily enhanced the rectus femoris. This indicated that different types of exercises target muscle growth in different areas.

Thus, this study proposes that future research explore the effects of specific exercises on inducing hypertrophy, with a focus on identifying elbow flexor exercises that promote greater growth in the proximal region. This information could inform the development of training protocols, designed to maximize biceps brachii hypertrophy by strategically pairing exercises such as the preacher curl with those targeting the proximal region.

Furthermore, from mechanistic standpoint, the previous study by Nosaka and Sakamoto (2001) investigated the magnitude of muscle damage to the elbow flexors from training at different elbow joint angle. They recruit 10 male students who were non-athlete to the study and employed the within subject-design. One arm was assigned to eccentric preacher curl exercise at short range of motion from 50^o to 130^o and the other arm was performing eccentric preacher curl at longer range from 100^o to 180^o of elbow flexion. The results demonstrated that the extent of muscle damage measuring from plasma creatine kinase at day 2-5 was significantly higher in the arm performing long eccentric range of motion (Nosaka and Sakamoto 2001). In this current study the participants were also instructed to always keep elbow on the supported pad of preacher curl machine and performed full range of motion as well, therefore coving range of 100^o to 180^o. This might be that they were also supposed to experience high magnitude of this exercise-inducing muscle damage as well.

According to the hypertrophic mechanism, some research suggested that exercise-induced muscle damage might play an important role in muscle remodeling (Hyldahl et al. 2017). Schoenfeld (2010) proposed that muscle damage could contribute to muscle hypertrophy by inducing satellite cell activation and proliferation. Physiologically, satellite cells were muscle stem cell situated between the basal lamina and the sarcolemma of skeletal muscle fibers, which, upon activation, could proliferate, and ultimately fuse with existing damaged fibers, thus leading to an increase in muscle fibers size (Harridge, 2007). Moreover, evidence showed that after chronic period of resistance training, for example in this current study, the numbers of satellite cells could increase compared to pre resistance training (Farup et al 2014). Moreover, failure-induced damage training could also stimulate the greater increase of muscle protein synthesis compared to low-damaged training (Burd et al. 2010). Although this study did not directly measure into cellular response level, previous study has demonstrated that when the resistance training covering wide range of eccentric range of motion, muscle protein synthesis significantly acutely elevated from baseline after training (Moore et al 2005).

Considering methodology, magnetic resonance imaging (MRI) is considering to be the gold standard in measuring muscle hypertrophy (Franchi et al 2018). However, this procedure is very expensive and the accessibility is very limiting when. In this study, the results from MRI demonstrated that muscle cross-sectional area significantly increased in every region in both TRAD and LLpBFR. Specifically, the percents of changes were □8.26%, □5.03%, □12.15% at proximal, middle, and distal regions, respectively in TRAD (all *p*<.05). Similarly, the percents of changes were □9.02%, □7.92%, □16.92% at proximal, middle, and distal regions, respectively in LLpBFR (all *p*<.05). The literature that employed MRI in measuring muscle cross-sectional areas of biceps brachii in this comprehensive manner in various regions was lacking, making direct comparison to other study was limited.

Our results demonstrated the interesting aspects of measurements from using both MRI and US. MRI measures muscle cross-sectional area while US measures muscle thickness. MRI can provide a more detailed evaluation as it captures the entire cross-sectional area of the muscle, offering comprehensive information about muscle size and structure. In contrast, US is a two-dimensional imaging technique that primarily measures muscle thickness, giving an indication of height from one end to the other end but not its full cross-sectional area. Therefore, while both methods are valuable, MRI gives a more complete picture of muscle morphology compared to the more limited view provided by US. Our MRI data set showed that muscle cross-sectional areas significantly increased in all regions (all *p*<.05), while muscle thickness showed a significant increase at only the middle and distal regions. Therefore, it is evident that

MRI provides a more comprehensive assessment of muscle growth across different regions, whereas US may only detect changes in certain areas.

When comparing between groups, MANOVA statistics showed that the Hotelling's Trace was .256 and p=.818 which was more than the significant level at .05, indicating that both resistance training protocols: TRAD and LLpBFR, resulted in similar morphological adaptation of biceps brachii muscle after 6-week programs.

When looking at program characteristics, it could be claimed that LLpBFR group that performed later sets with low intensity with blood flow restriction technique and high numbers of repetitions and longer time under tension per set, would technically induce more metabolic stress stimulus (Schoenfeld 2013). The average repetition performed in high intensity sets of this study were 9.5reps, 11.3reps, 10.6reps, 9.3reps, 13.5reps, and 14.7reps, respectively from week 1-6. In contrast, the average repetition performed in low intensity sets of this study were 23.5reps, 24reps, 28reps, 29.2reps, 35.5reps, and 36reps, respectively from week 1-6. These differences in numbers of repetitions were confirmed by the Independent Samples t-test, showing p-value =.000. The importance of metabolic stress stimulus which specifically referred to the accumulation of metabolites such as lactate and hydrogen ions within the working muscle (Schoenfeld 2013) was proposed in previous studies. It was claimed that metabolic stress could enhance muscle hypertrophy through various indirect mechanisms, such as inducing fatigue to recruit more motor units (Takarada et al. 2000), increasing hormonal release such as growth hormone (Dangott et al. 2000), and causing a cell-swelling effect (Loenneke et al. 2012). For example, Fink et al. (2018) found that low intensity resistance training (20RM), consisting of biceps curl and preacher curl exercises, combined with very short rest between sets (30s) significantly induced more metabolic stress markers as confirmed by acutely increasing in growth hormone and muscle thickness post-exercise as marker of cell-swelling (□7704.20%and □35.2% and, respectively).

Although this current study did not dive deep into collecting data of these mechanisms, the finding did not fully support these claims as the extent of muscle hypertrophy in LLpBFR group did not significantly exceed the TRAD group which was assigned to train with high intensity with just low to moderate repetitions. In contrast, this study supported the logical basis provided by Wackerhage's study (2018). It was proposed the most important stimuli that initiated skeletal muscle hypertrophy following resistance exercise was mechanical tension and its sensors (Wackerhage et al 2018). When muscles produce high force again external load either by heavy load or with high level of fatigue, the mechanoreceptors could detect the internal stress, signaling electrochemical cascades such as IGF-1/AKE/mTOR pathways and TGFβ/myostatin pathway (Sartori et al. 2021), stimulating muscle protein synthesis or decreasing muscle protein breakdown and resulting in hypertrophy (Burd et al 2012).

There was some previous study as well that compared between high intensity resistance training and low intensity resistance training with blood flow restriction and measured bicep brachii hypertrophy. For example, Thiebaud et al. (2013) recruited postmenopausal women and randomly assigned to a heavy elastic band training group (MH) or a light elastic band training group with BFR (LI-BFR). The results demonstrated that biceps brachii muscle thickness, measured at 60% of humerus length – corresponding to middle region, increased from 2.54cm to 2.57cm, □0.3mm, in MH and 2.67cm to 2.75cm, □0.8mm, in LI-BFR. For one reason that muscle thickness of biceps brachii did not increase that much might be because the participants did not train with biceps brachii exercise directly, but indirectly trained via exercises such as seated chest press, seated row and seated shoulder press which also involved biceps brachii activation. Nevertheless, the statistical significance was not reach in both groups. Another limitation to mention was that the difference between this current study and Thiebaud's was clearly the age of participants.

It was worth mentioning that this current study utilized the combined protocol which LLpBFR group did not train exclusively with low intensity, but they also had early sets of high intensity as well. This was novel, yet difficult to make direct comparison, because no previous study had implemented this style of training in the scientific literature before. The previous study that employed training structure was close, albeit different, to this current study was conducted by Yasuda et al. (2011).

The study compared between intensities and hypertrophic from bench pressing of high intensity 75%1RM and low intensity with blood flow restriction at 30%1RM as well as combined (Yasuda et al. 2011). Participants in this study were forty young healthy men, age 22-32 years. They were randomly assigned into of three groups. The first group training with 75%1RM for 3 days per week throughout 6-week program, the second group training exclusively with 30%1RM with blood flow restriction throughout program 3 days per week for 6 weeks, and the last group performed high intensity twice-weekly and low intensity once-weekly for 6 weeks. Muscle hypertrophy was assessed via MRI scans. However, they did not assess muscle hypertrophy of biceps brachii, but still measured hypertrophy of triceps brachii. The results demonstrated that the muscle cross-sectional area of triceps brachii significantly increased in all training group (all $p<.05$). Specifically, the cross-sectional area of the triceps brachii increased about □185mm^2 or 8.6%, □90mm^2 or 4.4%, and □155mm^2 or 7.2% respectively. Although Yasuda's program structure and assessed muscle were different to this current study, important similarity was that the combined protocols of ours resulted in significant increases in muscle hypertrophy metrics to the similar extent as high intensity resistance training. The sums of increase in muscle cross-sectional area of biceps brachii was 207mm^2 in TRAD and 256.5mm^2 in LLpBFR; similarly, the sums of increase in muscle thickness of biceps brachii was 1.03cm and 1.02cm in TRAD and LLpBFR, respectively.

Based on the aforementioned findings, it could be concluded that the preacher curl exercise significantly promoted hypertrophic adaptation, as evidenced by notable increases in both muscle thickness and muscle cross-sectional area of the biceps brachii.

Notably, regional muscle hypertrophy was predominantly observed in the distal region of the biceps brachii after six weeks of training, as confirmed by both MRI and ultrasound techniques. Furthermore, the preacher curl exercise appeared to be less effective in inducing hypertrophy in the proximal region, which aligned with previous research findings. Additionally, both TRAD and LLpBFR protocols produced similar hypertrophic outcomes and patterns, demonstrating that either method could serve as an effective alternative to the other.

Summary

This study provided evidence that the preacher curl exercise, performed using a preacher curl machine, was not particularly effective in eliciting proximal hypertrophy of the biceps brachii. The most significant muscle growth was observed in the middle and distal region of the muscle belly, which may be attributed to several factors. One such factor is stretch-mediated hypertrophy, as the biceps brachii is most activated when stretched during the preacher curl exercise. This loaded stretch can generate passive tension, potentially leading to increased muscle protein synthesis post-exercise, thereby promoting hypertrophy. Additionally, performing the preacher curl through a full range of motion, as done in this study, may induce a high degree of muscle damage, particularly when the muscle is stretched. Theoretically, muscle damage can also stimulate muscle protein synthesis, potentially enhancing hypertrophy through this mechanism.

2. Muscle cross-sectional area and muscle thickness of Vastus lateralis

The main findings of this study were that TRAD significantly increased muscle cross-sectional area, as measured via MRI, at all regions (□286.00mm^2, □222.30mm^2, □222.60mm^2, respectively from proximal, middle, and distal regions, all p<.05). In the same way, LLpBFR also demonstrated significantly increases in muscle cross-sectional area at all regions as well (□255.63mm^2, □245.63mm^2, □215.00mm^2, respectively from proximal, middle, and distal regions, all p<.05). Moreover, muscle thickness at middle and distal regions significantly increased (□0.32cm and □0.29cm, respectively, all *p*<.05) after training in TRAD and differently, muscle thickness at proximal and distal regions significantly increased (□0.63cm and □0.36cm, respectively, all *p*<.05) after training in LLpBFR.

The hypertrophic results in vastus lateralis muscle also reinforced what was claimed earlier in part of biceps brachii that muscle hypertrophy was non-uniform (Antonio 2000). Gryzlo et al. (1994) compared the vastus lateralis activation, via EMG, from knee extension exercise at different knee joint motions and found that during knee extension exercise, at the very end of knee extension phase (15^{o} – 0^{o} of knee extension), vastus lateralis and vastus medialis showed the highest activation compared to earlier extension phase (45^{o} – 30^{o} of knee extension). In this current study, the participants were instructed since the first session that they must perform knee extension in the manner of full range of motion; therefore, they must this range that muscle was activation the most as well. In contrast to preacher curl that biceps brachii was activated to the highest extent when muscle belly was fully stretched (Oliveira et al. 2013), vastus lateralis muscle was activated the most when muscle belly was almost fully shortened (Gryzlo et al. 1994). This might partially contribute to the significant increase in muscle hypertrophy around proximal regions of vastus lateralis. In this study, the increases in muscle cross-sectional area supported this hypothesis, demonstrating that muscle cross-sectional area significantly increase □286.00mm^2 in TRAD and □255.63mm^2 in LLpBFR at proximal region compared to □222.60mm^2 in TRAD and □215.00mm^2 in LLpBFR at distal end.

However, the finding in muscle thickness was confounding. The results demonstrated that muscle thickness at proximal region significantly increased only in LLpBFR group (□0.63cm, *p*=.014) but not in TRAD group (□0.18cm, *p*=.444). The reason for this non-significant, yet positive, increase might be the baseline characteristics of participants. Although there was no statistically significant difference at baseline between groups (F=.585, *p*=.456), the vastus lateralis thickness at the proximal region of TRAD group was initially thicker than that of LLpBFR (2.76±0.57cm vs 2.54±0.65cm, respectively).

The results of increases in vastus lateralis hypertrophy in this study agreed with previous studies which found that after the period of resistance training, vastus lateralis muscle significantly increases in size. For example, Lundberg et al. (2019) compared the regional hypertrophy of knee extensors from knee extension exercise using either flywheel or weight-stack machine. Sixteen men and women were recruited and within-subject design was employed. One leg of participants would be trained with flywheel and the other leg would be trained with weight-stack machine. Muscle hypertrophy was measured via MRI. After 8-week program, the results demonstrated that vastus lateralis cross-sectional area significantly increased in weight-stack machine training legs from 404.9cm^2 to 448cm^2 and 228.6cm^2 to 251.6cm^2 in male and female participants, respectively. In the same way, the leg training with flywheel also significantly increased in muscle cross-sectional area from 427.3cm^2 to 464cm^2 and 212.6cm^2 to 233.8cm^2 in male and female participants, respectively (Lundberg et al. 2019).

Another study that investigated the effect of knee extension exercise on vastus lateralis hypertrophy was conducted by Nobrega et al. (2018). The researcher recruited Thirty-two young men with no resistance training experience and randomly assigned training leg to one of 4 groups. The first leg group performed high intensity 80%1RM to failure, the second leg group performed 80%1RM as well but not to failure, the third leg group performed low intensity 30%1RM to failure, and the fourth leg group performed 30%1RM with stopping before failure. Training program lasted for 12 weeks with twice sessions weekly. Muscle cross-sectional area of vastus lateralis was measured using US technique, obtaining picture at 50% of the femur length which correspond to middle region in this current study. The results demonstrated that all training protocols induced similar hypertrophic effect in increasing vastus lateralis cross-sectional area after week 6 (□3–4.6%, ES=*Small*) and week 12 (□6.1–7.5%, ES=*Small*) (Nobrega et al. 2018).

It was interesting to compare the findings from the MRI results of this current study with those of Nobrega's study. This study showed significantly higher increases in muscle cross-sectional area at middle region of vastus lateralis, with TRAD and LLpBFR groups experiencing gains of 8.68% and 9.01%, respectively, compared to only 3-4.6% in Nobrega's study. This discrepancy might be explained by the differences in training intensity and volume. In the current study, the number of training sets progressively increased from 3 sets in week 1 to 8 sets in week 6, whereas Nobrega's study maintained a consistent 3 sets in all training sessions. This difference in program intensity likely contributed to the greater muscle growth observed in the current study.

A recent study found that training knee extension at the initial phase of motion could induce more hypertrophy in the vastus lateralis muscle (Pedrosa et al. 2022). In this study, untrained healthy participants were randomly assigned to either a group that performed knee extensions within the initial range of motion (100° to 65° of knee extension) or a group that performed knee extensions through the full range of motion (100° to 30°, with full knee extension being 0°). After a 12-week training program, the cross-sectional area of the vastus lateralis was measured using ultrasound. The results showed that at 50% of femur length, the vastus lateralis cross-sectional area increased by approximately 16% and 14% for the initial range and full range groups, respectively. At 70% of femur length, the increases were about 19% and 12%, respectively (Pedrosa et al. 2022). This study was the first to demonstrate that performing knee extension exercises within the initial range of motion could lead to greater hypertrophy of the vastus lateralis than exercises performed through the full range of motion.

When comparing these findings to the current study, the hypertrophy observed in Pedrosa's study was greater at both regions of the muscle. In the current study, the middle region increases in cross-sectional area were 8.68% for TRAD and 9.01% for

LLpBFR, while Pedrosa's study showed increases of 16% and 14%, respectively. Similarly, at the distal region, the increases were 14.02% for TRAD and 12.68% for LLpBFR, compared to 19% and 12% in Pedrosa's study. The longer training duration in Pedrosa's study (12 weeks compared to 6 weeks in the current study) might partially explain these differences.

If we rely on the mechanism of muscle hypertrophy, the finding in Pedrosa's study might be partially explained by the degree of muscle damage happening from keeping training knee extensors in the lengthened position (Schoenfeld 2012). Previous study demonstrated that after performing eccentric knee extension at range of motion from 90^{o} -20^{o} (0^{o} = full extension), serum creatine kinase significantly increased after training up to 168 hours (Hicks et al 2016). As mentioned earlier, the occurrence of muscle damage could induce satellite cell activity and stimulate the remodeling of muscle structure which might contribute to muscle hypertrophy in the long-term (Kaczmarek, et al. 2021).

Moreover, it was demonstrated in previous study that not only intramuscular regional hypertrophy occurred as a result of resistance training, intermuscular differences of muscle hypertrophy were also significant in quadriceps group. Narici et al. (1996) investigated the effects of very long-term training, 6 months, using knee extension exercise at intensity 80%1RM. Seven healthy young males were assigned to training program that they must train every other day throughout 6 months. Muscle hypertrophy was assessed via MRI measuring muscle cross-sectional area of individual knee extensor. The results demonstrated that total quadriceps cross-sectional area at the proximal region increased 18.8%, compared to only 13% increase in distal region, which this finding also corresponded to the findings in our study that vastus lateralis area increased to higher extent at proximal region than distal end. Moreover, their results also demonstrated that rectus femoris was the muscle that hypertrophied (□27.9%), followed by vastus lateralis (□19.5%) and vastus medialis (□18.7%) and lastly vastus intermedius (□17.4%) (Narici et al. 1996).

When comparing between groups, MANOVA statistics showed that the Hotelling's Trace was .109 and *p*=.970 which was more than the significant level at .05, indicating that both resistance training protocols: TRAD and LLpBFR, resulted in similar morphological adaptation of vastus lateralis muscle after 6-week programs.

This study was novel in its program design, with the LLpBFR group training with half of the total volume at the intensity of 70%1RM and the other half at 30%1RM with using a practical blood flow restriction technique. Since no previous studies had ever implemented a program design like this, making direct comparisons to past research findings was challenging. However, number of previous study existing that they only compared high intensity resistance training only to low intensity resistance training only with blood flow restriction and using knee extension exercise.

For example, Ellefsen et al. (2015) compared the hypertrophic effects of high intensity 74-92%1RM and low intensity with blood flow restriction 30%1RM training, using knee extension exercises and within-subject design. Fifteen healthy untrained female participants were recruited to the study. One random leg of the participants was assigned to training with blood flow restriction protocols for 5 sets to failure and 45 seconds rest between set. Another leg of participants was assigned to training with 3 sets of high intensity that progressively increased from 74%1RM in the first week to 92%1RM in week 12. Both training protocols trained twice weekly. After 12-week program, vastus lateralis cross-sectional area was measured via MRI scan. The results demonstrated that vastus lateralis cross-sectional areas at the proximal and distal regions increased similarly in both high intensity training legs and low intensity training legs (□8% vs □7%, and □7% vs □10%, respectively). When comparing to proximal and distal regional hypertrophy of this current study, the extent of increases were very close in relative percent (□11.48% vs □14%, in proximal and distal regions of TRAD, respectively and □10.80% vs □12.67% in proximal and distal regions of LLpBFR, respectively). The possibility was that this study recruited untrained male participants compared to females in Ellefsen's study; therefore, the little higher response of muscle growth might be expected.

Additionally, another early study conducted by Kubo et al. (2006) employed a within-subject research design, recruiting healthy young male participants. Each participant had one leg randomly assigned to low-intensity training (20% 1RM) with blood flow restriction and the other leg to high-intensity training (80% 1RM). Both legs performed unilateral knee extension exercises within a range of motion from 90° to full knee extension (0°), similar to the current study. Participants trained three times per week for 12 weeks. After the program, muscle hypertrophy of the vastus lateralis was measured using MRI scans. The results showed a significant increase in the cross-sectional area of the vastus lateralis: 6.1% (*p*=.024) in the low-intensity training leg and 7.5% (*p*=.021) in the high-intensity training leg. Notably, the low-intensity training did not require participants to train to failure; instead, they completed 4 sets of 25, 18, 15, and 12 repetitions (Kubo et al. 2006). Despite not training to failure, the hypertrophic results were still significant, suggesting that training to failure may not be necessary when using a blood flow restriction training protocol.

Moreover, Laurentino et al. (2012) conducted an interesting study by recruiting 29 healthy young male participants and randomly assigning them to one of three groups: high-intensity training, low-intensity training, or low-intensity training with blood flow restriction. The training protocol consisted of knee extension exercises with a similar range of motion to this study, performed over a total of 8 weeks. During the first 4 weeks, participants performed 3 sets, and during the last 4 weeks, they performed 4 sets. The muscle cross-sectional area of the quadriceps was measured via MRI at 50% of the femur length. The results showed that muscle cross-sectional areas increased by 6.1% (*p*=.0004) in the high-intensity group and by 6.3% (*p*=.0007) in the low-intensity with blood flow restriction group. However, the low-intensity group showed only a slight increase of about 2% from baseline. Comparing Laurentino's findings to this study was challenging because the MRI scans in this study were conducted on the individual vastus lateralis muscle, not the entire quadriceps muscle. Nevertheless, the extent of increase in the middle region of the vastus lateralis in this study was still similar to Laurentino's findings, with reported increases of □8.6% in TRAD and □9.1% in LLpBFR.

From a molecular perspective, Laurentino et al. (2012) reported that the MSTN or myostatin gene was significantly decreased in both the high-intensity (-41%, $p<.0001$) and low-intensity with blood flow restriction (-45%, $p=.0004$) groups. Myostatin was a gene related to the regulation of muscle growth, acting as a negative regulator that limits the extent of muscle hypertrophy (Thomas et al. 2000). Specifically, Myostatin could inhibit muscle differentiation and growth by signaling through the Activin receptor type IIB pathway, reducing muscle cell proliferation and protein synthesis (Babcock et al. 2015). Therefore, the observed decrease in myostatin levels suggested that both high-intensity and low-intensity training with blood flow restriction could effectively reduce the inhibitory effects of myostatin (Laurentino et al. 2012). This reduction in myostatin levels might partially contribute to the enhanced muscle hypertrophy observed in these training protocols. These findings highlighted the potential of blood flow restriction training to achieve significant muscle size adaptations, even at lower intensities.

Moreover, Haun et al. (2017) demonstrated that resistance training programs at high intensity (80% 1RM) and low intensity (30% 1RM) elicit similar acute post-exercise molecular responses in terms of mRNA expression and phosphoproteins associated with muscle hypertrophy. The researchers employed a cross-over design, where the same group of participants performed two different knee extension protocols: 80% 1RM to failure and 30% 1RM to failure. Following each exercise bout, a biopsy of the vastus lateralis muscle was collected to analyze the molecular responses under each load condition. The results indicated that both load conditions resulted in similar expression levels of phosphoproteins related to muscle hypertrophy, such as p-mTOR, p-70S6K, p-4EBP1, and p-AMPK, despite the differing intensities (Haun et al., 2017). This suggests that muscle hypertrophy can be achieved with varying intensities of resistance training, provided the exercise is performed to failure. Although our study did not investigate the acute molecular response post-training, our findings supported the logic of similar muscle growth outcomes between TRAD and LLpBFR training.

Another study that compared high intensity resistance training to exclusively low intensity resistance training with blood flow restriction was conducted by Martin-Hernandez et al. (2013). This study aimed to investigate muscle hypertrophy adaptations after two different volumes of blood flow restriction training and compare them with high-intensity training. Thirty-nine recreationally active male university students were recruited and randomly assigned to one of three groups: 1) low-volume low-intensity blood flow restriction group, 2) high-volume low-intensity blood flow restriction group, and 3) traditional high-intensity training group. The training program lasted 5 weeks with 2 sessions per week. Low intensity was fixed at 20% 1RM, while high intensity was set at 85% 1RM. Interestingly, Martin-Hernandez and team used a fixed repetition scheme for the blood flow restriction groups instead of training to failure. The low-intensity groups performed 1 set of 30 repetitions followed by 3 sets of 15 repetitions, with the high-volume group repeating this scheme twice per session. Vastus lateralis thickness was measured using ultrasound at 50% of the femur length, corresponding to the middle region of the muscle. The results showed that all training groups significantly increased vastus lateralis thickness by about 9.9% (p<.001). This study indicated that doubling the exercise volume in the low-intensity group did not provide any additional hypertrophic benefit, highlighting that a lower volume of blood flow restriction training could be as effective as higher volumes and high-intensity training for muscle hypertrophy.

Comparing Martin-Hernandez's study to the current findings, the extent of vastus lateralis thickness increased in the middle region was 15.24% and 13.39% in the TRAD and LLpBFR groups, respectively. These percentage increases were not drastically different from the 9.9% reported by Martin-Hernandez et al. (2013). However, our training design differed significantly. In our study, all participants trained to failure in every set, even with low-intensity blood flow restriction. The average number of repetitions performed in the high-intensity sets was 13.9±4.5 repetitions, while in the low-intensity sets, it was 42.6±24.4 repetitions. Most importantly, the low-intensity group in this study did not train exclusively with low-intensity sets, as half of their volume consisted of high-intensity sets. This difference in training approach might account for the higher percentage increases observed in our study.

From a hypertrophy mechanism point of view, a training program that combines both high and low-intensity sets should be ideal when creating hypertrophy-focused training program because it targets both key factors essential for muscle growth: mechanical tension and metabolic stress (Schoenfeld 2010). This notion was also supported by previous study (Helms et al. 2014). High-intensity sets primarily induce high mechanical tension which can lead to muscle damage and the activation of satellite cells, which in turn contribute to muscle repair and growth (Kadi et al 2004). The heavy loads used in these sets ensure maximal muscle fiber recruitment, particularly of the type II fibers that have the greatest potential for growth (Fry 2004). On the other hand, low-intensity sets with blood flow restriction which is considered to be high volume training focus on generating metabolic stress (Gonzalez et al. 2015). Metabolic stress increases as the result of the accumulation of metabolites such as lactate, which can enhance muscle growth through various pathways, such as cell swelling, increased anabolic signaling, and the production of growth factors (Freitas et al. 2017). This dual approach ensures that the muscle is subjected to a comprehensive stimulus, maximizing hypertrophic adaptations. Therefore, combining both high and low intensity training protocols should provide a balanced strategy for muscle hypertrophy.

Furthermore, similar to the non-uniform muscle hypertrophy observed with preacher curl exercises—both within individual muscle regions and across different muscles—it was advisable for bodybuilders to incorporate various exercises to stimulate hypertrophy in different muscle regions. This approach ensures comprehensive muscle development and helps address potential imbalances in muscle growth. Evidence from previous studies supported this recommendation. For example, squats have been shown to be highly effective for inducing vastus medialis hypertrophy but were ineffective for targeting the rectus femoris (Kubo et al., 2019). On the other hand, leg extensions primarily enhanced the hypertrophy of the rectus femoris (Zabaleta-Korta et al., 2021) and vastus lateralis, as demonstrated in the current study. Additionally, the leg press induced greater hypertrophy in the distal region of the quadriceps compared to the proximal region (Franchi et al., 2014) and while hamstrings muscle such as biceps femoris long head was better hypertrophied by seated leg curl, biceps femoris short head was better hypertrophy by Nordic hamstring curl (Maeo et al., 2024). Putting in application, a clear example of the benefits of varying exercises was illustrated by Costa et al. (2021). Their study found that the anterior thigh hypertrophied more comprehensively when different lower body exercises were incorporated. Specifically, they observed increases of 4.5mm, 2.3mm, and 2.5mm in the proximal, middle, and distal regions of the muscle, respectively, with a program consisting of leg press, half squat, and hack machine exercises. In contrast, a program consisting solely of leg press resulted in smaller increases of 2.3mm, 1.1mm, and 2.5mm in the same regions, respectively.

Drawing from the aforementioned findings, it could be inferred that both the TRAD and LLpBFR protocols yielded comparable hypertrophic outcomes in the vastus lateralis muscle hypertrophy, evidenced by increases in both muscle cross-sectional area and thickness. Therefore, either training protocol could serve as an alternative to the other. However, greater absolute increases in muscle cross-sectional area were predominantly observed in both the TRAD and LLpBFR groups. This phenomenon might be partially attributed to the fact that the highest muscle activation of the vastus lateralis occurred when the knee extensors were most shortened at the end of the concentric phase of the knee extension exercise. This high muscle activation during the shortened phase likely contributed significantly to muscle growth in these protocols.

Summary

This study revealed that hypertrophy in the vastus lateralis during resistance training was influenced by several key factors. One critical factor is the peak force generated when the muscle is in its most shortened position, which likely contributes to the hypertrophic response through high mechanical tension. Additionally, the full range of motion performed in both groups induced stretch-mediated hypertrophy, particularly when the muscle was fully stretched. This stretch creates significant muscle damage, which is known to stimulate muscle protein synthesis and promote hypertrophy. The hypoxic environment in LLpBFR, combined with the reduction of myostatin, further enhances hypertrophy and training to failure can stimulate activation of specific signaling pathways, including p-mTOR, p-70S6K, p-4EBP1, and p-AMPK. These pathways are crucial for protein synthesis and muscle growth. Moreover, the LLpBFR program is considered ideal due to its ability to replicate the complex interplay of mechanical tension, metabolic stress, and muscle damage.

3. Vastus lateralis architecture

The main findings about vastus lateralis architecture in this study were that both TRAD and LLpBFR significantly increased fascicle length of vastus lateralis after 6-week programs (□12.13mm, p=.013 and □11.81mm, p=.013, respectively). Interestingly, statistically significant increase in fascia thickness was observed only in the LLpBFR group (□0.55cm, p=.026), but not in TRAD. Nevertheless, both groups demonstrated slightly increases, albeit non-significant, in fascicle angles of vastus lateralis (□1.79degree, p=.277 and □2.90degree, p=.105, respectively).

Physiologically, these significant increases in fascicle length are the indicative of an architectural adaptation within the muscle, involving the addition of sarcomeres, which are the fundamental contractile units of muscle fibers, in series (Pincheira et al. 2021). This addition of more sarcomeres substantially affects the muscle fibers resting length and length-tension characteristics of muscle (Wisdom et al. 2015). Firstly, the increase in sarcomere number alters the muscle's length-tension relationship, which describes how the force a muscle produced changes with variations in muscle length (Brughelli & Cronin 2007). By adding sarcomeres in series, the muscle could operate efficiently over a greater range of lengths because the optimal overlap of actin and myosin filaments could be maintained across a broader range of muscle extensions and contractions (Kruse et al. 2021).

Secondly, the increase in fascicle length enhanced the muscle's shortening speed (Wisdom et al. 2015). With more sarcomeres arranged in series, each sarcomere underwent a smaller degree of shortening for a given overall muscle contraction; consequently, the contraction speed of each individual sarcomere was additive, leading to a faster overall shortening speed of the muscle fascicle (MacDougall and Sale, 2014). This could be very beneficial in power sport which required muscle to produce high force and shorten very quickly (Harris-Love et al. 2021).

In this current study, knee extension training using both protocols led to substantial increases in fascicle length (□16.85% in TRAD and □15.97% in LLpBFR), aligning with findings from previous studies employing knee extension exercises to observe architectural adaptations. For example, Valamatos et al. (2018) used a within-subject research design to investigate whether full range of motion training (FULL) would result in similar architectural adaptations compared to partial range of motion training (PART). They recruited 19 male college students and randomly assigned one leg of each participant to FULL, which involved knee extension exercises on isokinetic machine from 100° to 0°, with 0° representing full knee extension, and the other leg to PART, which involved similar exercises from 60° to 0° of knee extension. After 15 weeks of training, vastus lateralis architectures were measured via ultrasound, with longitudinal images taken from the mid-belly muscle at 39% of femur length. The findings showed a significant increase in fascicle length only in the FULL group (□4.9%, $p<.001$), with no change observed in the PART group.

Besides, another previous study conducted by Franchi et al. (2014) reported similar gains in fascicle length after leg press resistance training at knee extension angle about 100° to 0°. The researcher investigated the architectural adaptation to concentric (CON) and eccentric (ECC) resistance training in human skeletal muscle. The study recruited 12 young males who performed 10 weeks of either CON training group and ECC training group. Vastus lateralis fascicle length was evaluated by ultrasonography. After 10 weeks of training, significant changes were observed in muscle architecture that during ECC exercises, muscle fascicle length increased by 12% ($p<.0001$) whereas CON exercises resulted in 5% ($p<.01$) increase in fascicle length. These distinct adaptations suggested that different types of mechanical stimuli (lengthening vs. shortening) lead to specific architectural changes in the muscle.

Besides, Franchi's study also reinforced the evidence of regional hypertrophy that they found that in the CON group, vastus lateralis hypertrophy was significantly observed in the middle region (□11%, $p<.01$), higher extent than ECC group (□7%, $p<.01$). In contrast, muscle hypertrophy was more evident in distal region in ECC group compared to CON group (□8% vs □2%, $p<.05$). This finding also suggests the importance of exercise selections and contraction types for those who aim to maximize hypertrophic outcome in quadriceps muscle.

Another study that employed knee extension exercises and demonstrated changes in fascicle length was conducted by Alegre et al. (2014). Twenty-eight healthy participants were randomly assigned to one of two groups: one group performed isometric knee extension at 90° of knee flexion (K90), and the other group performed knee extension at 50° of knee flexion (K50). This study was unique in that it employed isometric movements, in contrast to the current study, yet covered the knee angles used here. After 8 weeks of training, fascicle lengths were measured via ultrasound at the mid-thigh location. The results showed a 4.2% increase (□3.2 mm) in fascicle length in the K90 group but not in the K50 group (□-0.3%).

Additionally, Alegre and colleagues also collected data on muscle thickness from the vastus lateralis at 25%, 50%, and 70% of the femur. The results indicated non-uniform hypertrophy of the vastus lateralis. At the proximal region, vastus lateralis thickness significantly increased by 0.21cm and 0.12cm in the K90 and K50 groups, respectively (all $p<.05$). In the middle region, the increases were 0.29cm and 0.11cm, respectively (all $p<.05$). Interestingly, at the distal region, muscle thickness increased only in the K90 group (□0.18 cm, $p<.05$), which trained isometrically at a longer muscle length. These findings support the idea that knee extension exercises preferentially induced muscle hypertrophy in proximal regions and that regional hypertrophy was evident from such exercises.

In the same way, Noorkoiv et al. (2014) examined angle-specific neuromuscular adaptations in response to isometric knee extension training at short muscle length and versus long muscle lengths (38° and 89°, respectively). They recruited sixteen men and randomly assigned them to one of two groups, training for three times a week for 6 weeks. Participants performed training of 5 sets of five 5 seconds maximal voluntary isometric contractions on an isokinetic machine. The fascicle lengths of vastus lateralis was measured in the very comprehensive manner at 33%, 50%, and 66% of femur length. The results demonstrated that the sum increase in fascicle length of the vastus lateralis muscle was greater when knee extensors were trained isometrically at long muscle lengths, involving exerting high force when muscle was stretched, compared to training at short muscle lengths (□10.9mm versus □8.6mm, respectively).

McMahon et al. (2014) provided the possible mechanism that training knee extension at long muscle length might be superior by demonstrated that when compared two groups of participants, one training knee extension at shortened position (50^{o}-0^{o} knee extension) and one training at lengthened position (90^{o}-40^{o} knee extension), they found that after 8 weeks of training, insulin-like growth factor 1 which was the important stimulus to induce muscle hypertrophy was released to higher extent (□31%, *p*.033) in lengthened position group compared to shortened position group (□7%, *p*=.438). Moreover, the researchers also examined the fascicle length changes of vastus lateralis at proximal (25%), middle (50%), and distal (75% of femur length) regions and found that in lengthened position group, fascicle length significantly increased in all regions (□27mm, □21mm, and □24mm, respectively). While the extent of increases was smaller in shortened position group (□18mm, □9mm, and □12mm, respectively).

When comparing the findings of this study to McMahon's, the at the proximal region of vastus lateralis, the fascicle length in this study increased to the smaller extents in either TRAD and LLpBFR (□12.13mm and □11.81mm, respectively) compared to lengthened position group or shortened position group (□27mm and □18mm, respectively). Training duration might play the significant role here, as in this study participants only trained for one session per week, compared to 3 sessions per weeks in their study. Therefore, this made total session far different (6 session vs 24 sessions) and the duration difference was 6 weeks vs 8 weeks.

Another recent study was conducted by Walker et al. (2020). This study investigated whether super-heavy eccentric-load training performed during the eccentric phase of lower limb strength training led to greater adaptations in muscle architecture compared to traditional strength training that used equal loads during both concentric and eccentric phases. In this study, 28 healthy young male participants with an average of 2.6 years of training experience were recruited. They were randomly allocated to three groups: accentuated eccentric-load training (AEL), traditional strength training (TRAD), or a control group. The AEL group performed leg press and knee extension exercises with a 40% greater load during the eccentric phase compared to the concentric phase. After a 10-week program, vastus lateralis fascicle length was measured via ultrasound at 50% of femur length. The results demonstrated that fascicle length significantly increased in the AEL group ($p<.05$) but not in the TRAD group (□13.7 mm vs. □0.7 mm, respectively). This study provided insight into the effectiveness of eccentric overload in enhancing muscle architecture (Walker et al. 2020). The significant increase in fascicle length observed in the AEL group suggested that the mechanical tension associated with heavier eccentric loads, when muscles were stretched, was the effective stimulus for promoting the addition of sarcomeres in series.

Additionally, the adaptation of fascicle length following strength training was observed across various muscles in both the upper and lower extremities. The previous study also reported a significant increase of approximately 9% in fascicle length of the triceps belly after 6 weeks of triceps cable pushdown training (Stasinaki et al. 2018), suggesting that all pennate muscles might have the potential to increase fascicle length following a period of strength training. Furthermore, the insights about the relationship between fascicle length and muscle hypertrophy was questioned by some previous study (Fukutani and Kurihara 2015). They conducted a comparison between two groups of participants, one trained and one untrained, using ultrasound imaging to assess muscle size and fascicle length. Surprisingly, despite the greater muscle thickness observed in the resistance-trained participants, both groups exhibited similar fascicle lengths. This indicates that fascicle length might not always accurately reflect muscle size or hypertrophy; nevertheless, this hypothesis was challenged by this current study finding, as the results demonstrated that both TRAD and LLpBFR significantly increased vastus lateralis fascicle length (□12.13mm and □11.81mm, respectively) together with muscle cross-sectional area (□286mm^2 and □255.63mm^2, respectively) and muscle thickness (□0.63cm and □0.18cm, respectively) at proximal region. Further investigation was warranted to fully understand the relationship between fascicle length and muscle size in the context of resistance training adaptations.

Appealingly, the previous stretching study also demonstrated the results of increased fascicle length of pennate muscle such as calf muscle after period of training as well. For example, Simpson et al. (2014) investigated the effect of static stretching in gastrocnemius muscle, performing 5 days per week for 6 weeks. They employed within-subject design which the nondominant plantar flexors of participants were stretched while the contralateral leg served as the controls. Leg press machine was employed in helping stretching calf muscle with additional load to ensure passive muscle stretch. Fascicle lengths were measured via US, from the lower aponeurosis to the upper aponeurosis. The results demonstrated that fascicle length of lateral gastrocnemius muscle significantly increased from baselined when measured at 1 week post intervention (about □10mm, $p<.001$).

Collectively, the studies indicated that knee extension exercises involving a full range of motion significantly contributed to increases in fascicle length. Valamatos et al. (2018) demonstrated that training through a full range of motion (100° to 0°) resulted in a significant increase in fascicle length compared to partial range of motion training (60° to 0°). Similarly, Franchi et al. (2014) showed notable increases in fascicle length with eccentric training yielding greater changes than concentric training. Besides, Alegre et al. (2014) found that isometric knee extension at 90° of knee flexion increased fascicle length, unlike training at 50°. Similarly, Noorkoiv et al. (2014) reported greater fascicle length increases when training isometrically at longer muscle lengths (89°). Then, Walker et al. (2020) highlighted the effectiveness of eccentric overload training in significantly increasing fascicle length more than traditional strength training. And last but not least, Simpson et al. (2014) demonstrated that static stretching of the gastrocnemius muscle led to increased fascicle length, emphasizing the impact of muscle stretching and passive tension.

The consistent finding across these studies was that training at longer muscle lengths or through a full range of motion effectively stimulated increases in fascicle length. This effect was likely due to the mechanical tension and muscle stretching, which promoted the addition of sarcomeres in series (Wisdom et al 2015). The stretch-induced tension during eccentric phases or isometric holds at longer lengths appeared to be a potent stimulus for fascicle elongation. Although this study did not use isometric or accentuated eccentric loading methods, both TRAD and LLpBFR protocols maintained a full range of motion during knee extension training, ensuring muscles were engaged at their maximal length. This likely explained the significant increases in fascicle length observed in both groups.

Moreover, it was worth noting that the stimuli from TRAD and LLpBFR suggested that the increase in fascicle length might be ROM-dependent. In this study, both TRAD and LLpBFR protocols increased fascicle length to a similar extent (*p*=.013), with no significant difference between the two groups as showed by MANOVA statistics, the Hotelling's Trace value =.045, *p*=.897. The TRAD group trained with heavy load high-intensity sets consistently, while the LLpBFR group alternated between heavy load and light load sets with blood flow restriction. This suggested that the full range of motion or muscle excursion range, rather than the specific load or intensity, might be the critical factor driving fascicle length increases (Valamatos et al. 2018). The consistent engagement of muscles at their maximal length during knee extension exercises likely provided sufficient mechanical tension and mechanical stretch, promoting the addition of sarcomeres in series regardless of the loading protocol. This finding aligned with previous research indicating that muscle stretching and passive tension at long lengths were potent enough to stimulate fascicle elongation, highlighting the importance of full ROM exercises in resistance training programs.

Moreover, the findings about fascia thickness in this study was very interesting to discuss. The statistically significant increase in vastus lateralis fascia thickness was observed only in LLpBFR group (□0.55mm, *p*=.026). However, there was slightly, albeit non-significant, increase in fascia thickness in TRAD group (□0.36mm, *p*=.081). Although there was no significant different between groups at baseline as showed that F=2.156 and *p*=.161, the baseline value of TRAD group was clearly thicker than that of

LLpBFR (1.26±0.46 vs 0.98±0.34, respectively). This might explain the non-significant p-value at post intervention.

After strength training program, it was documented that there would be the remodeling of extracellular matrix (ECM) (Wisdom et al. 2015). The adaptation of ECM volume, structure, as well as mechanical stiffness adapted in response on mechanical stimuli during the resistance training program. Although this study did not dive into molecular responses of specific increase of collagens, Kjaer et al. (2004) explained that the ECM responded to mechanical loading by remodeling to support hypertrophy and increased mechanical demands. The ECM, especially collagen-rich connective tissue, ensured effective force transmission and structural integrity. Resistance training significantly boosted ECM turnover by increasing collagen synthesis, particularly type I and type III collagens, and metalloprotease enzyme activity, regulated at multiple levels and enhanced by growth factors post-exercise. Chronic mechanical loading resulted in increase of collagen turnover and synthesis, improving the tissue's mechanical properties and load resistance. Moreover, Mechanical loading rapidly alters ECM properties through activated signaling pathways, driven by growth factors such as TGF-beta, Insulin-like growth factor, IL-1, IL-6, FGF, and VEGF, supporting hypertrophic responses (Kjaer et al. 2004).

For one mechanism that could explain the observed effects of blood flow restriction on fascia remodeling, it was essential to consider the potential role of local hypoxic factors, such as hypoxia-inducible factor (HIF). Torpel et al. (2018) highlighted that BFR might induce localized hypoxia within the muscle tissue due to restricted blood flow, leading to the activation of HIF pathways. Hypoxia-inducible factor has been implicated in various cellular responses to low oxygen levels, including angiogenesis, metabolism, and tissue remodeling (Torpel et al. 2018). In the context of fascia remodeling, the activation of HIF signaling pathways in response to BFR-induced hypoxia might trigger adaptive changes in fascial thickness and composition. Moreover, studies suggested that hypoxic conditions could stimulate collagen synthesis and remodeling processes within connective tissues (Liu et al., 2013). Admittedly that tendon was mainly composed of collagen protein, recent meta-analysis had demonstrated that low intensity with blood flow restriction resistance training was so effective to induce tendon hypertrophy after at least 8 weeks of intervention (Bechan Vergara et al., 2023). Therefore, it was possible that the observed increases in fascia thickness following blood flow restriction training such as from this study (□55.10%) could be mediated, at least in part, by hypoxia-induced alterations in collagen metabolism and turnover. However, further research was warranted to elucidate the specific molecular mechanisms underlying the effects of BFR on fascial remodeling and to validate the role of HIF signaling in this process.

Moreover, another mechanism that possibly explained the findings of this study was related to metabolic-stress-induced growth hormone release. It was well-documented in resistance training literature that strength training programs with high repetitions and longer time under tension induced more acute growth hormone release during and after exercise. For example, Jakobsson et al. (2021) demonstrated that a training program characterized by full-body exercises performed at 60–70% 1RM for 10–15 repetitions, with short one-minute rest intervals, resulted in higher peak growth hormone release compared to a program with 80–90% 1RM for 4–6 repetitions with three-minute rest intervals (8.00 µg/L vs. 5.76 µg/L, respectively) in both males and females. Similarly, Vilaca-Alves et al. (2022) found that when half squat and bench press exercises were performed with blood flow restriction techniques at 20%1RM for 4 sets of (30, 15, 15, and 15 repetitions, respectively), post exercise growth hormone released increased significantly up to 1464% and 2379% at immediately and 15minutes post exercise, respectively.

In a previous study, Doessing et al. (2010) found that growth hormone injections directly stimulated collagen synthesis after 14 days of administration. They observed a 3.9-fold increase in tendon collagen type I mRNA expression and a 1.3-fold increase in tendon collagen protein synthesis ($p<.01$ and $p=.02$, respectively). Additionally, muscle collagen I mRNA expression and muscle collagen protein synthesis increased by 2.3-fold and 5.8-fold ($p<.01$ and $p=.06$, respectively). Therefore, it was possible that the LLpBFR training program, designed to induce more metabolic stress, resulted in a higher extent of growth hormone release compared to low-repetition heavy resistance training (TRAD). This continuous stimulation and accumulation of post-exercise growth hormone release might have stimulated collagen synthesis, as evidenced by the significant increase in fascia thickness observed only in the LLpBFR group in this study. However, this study did not directly examine the post-exercise hormonal release of both protocols. Future studies should investigate the growth hormone responses to these specific regimens, TRAD and LLpBFR, to better understand the mechanisms underlying the observed differences in fascia thickness.

Recently, the logical hypothesis that thickened connective tissue might impede skeletal muscle growth has been previously proposed (Roberts et al., 2018). This notion found support in animal studies where the removal of cardiac fascia led to a substantial increase in heart hypertrophy within a relatively short timeframe (Hammond et al., 1992). Additionally, another animal study demonstrated that mice exhibiting maladaptation, characterized by an overexpression of specific types of collagen mRNA experienced impaired hypertrophic responses to overload training (White et al., 2009).

Contrary to these theoretical considerations, this present study yielded findings that were worthy of consideration. Despite observing increases in fascia thickness in TRAD and LLpBFR (□55.10% and □28.57 respectively), concurrent muscle hypertrophy as showed by increase muscle thickness (□6.52% and □24.08%, respectively) and muscle cross-sectional area (□11.49% and □10.08%, respectively) of similar region was evident. Consequently, the findings in this current did not support the hypothesis that heightened fascia thickness serves as a limiting factor for muscle hypertrophy (Roberts et al., 2018).

Furthermore, our study aligned with the conclusions drawn by Godwin et al. (2023), indicating that fascia thickness content did not differ between individuals showing high or low responses to hypertrophy training. The researcher recruited thirty-eight untrained male participants and assigned them to 10-week full-body style resistance training program. Participants trained twice weekly throughout the program. After 10 weeks of training, muscle and fascia thickness of vastus lateralis was measured via US technique, similar to this study, at 50% of femur length. Muscle mass change was measured via computed tomography scan at mid-thigh as well. The results demonstrated that mid-thigh cross-sectional area and vastus lateralis muscle significantly increased from baseline in the group of high responders (about □200mm^2 and □0.6cm respectively). In contrast, low responders observed no change in hypertrophic metrics, with statistically significant different between group (p<.001). Nevertheless, the fascia thickness of vastus lateralis did not significantly differ between group from pre to post training. The average fascia thickness of high and low responders was 1.2mm and 1.3mm, respectively at post intervention.

Interestingly, when compared to Godwin's study, the relative fascia thickness between this current study and theirs was quite similar, the average vastus lateralis fascia thickness of TRAD and LLpBFR in this study at pre intervention was 1.26mm and 0.98mm, respectively compared to about 1.4mm and 1.2mm in high responders and low responders, respectively, in Godwin's study. However, at post intervention, fascia thickness increased substantially in both group of this study to 1.62mm and 1.52mm, respectively. In contrast, the fascia thickness of Godwin's study remained quite same, 1.2mm and 1.3mm, respectively at post intervention.

Therefore, the findings of this study offered valuable insights into the role of blood flow restriction training (LLpBFR) and traditional resistance training (TRAD) on fascia thickness and muscle hypertrophy. The significant increase in vastus lateralis fascia thickness observed in the LLpBFR group and the non-significant increase in the

TRAD group suggested that localized hypoxia and metabolic stress from BFR might enhance collagen synthesis and ECM remodeling. Despite the increased fascia thickness, both groups experienced muscle hypertrophy, contradicting the hypothesis that thicker fascia might impede muscle growth. Future research should further explore the molecular mechanisms, particularly the role of growth hormone and hypoxia-inducible factors, in fascia and muscle adaptations to different training regimens.

Summary

Both groups significantly increased muscle fascicle length, which could be attributed to key training factors such as full range of motion and eccentric loading. Both groups performed knee extensions with full stretching during the eccentric phase, which was crucial for inducing sarcomerogenesis and increasing fascicle length. The eccentric phase also represented an overload, further stimulating this adaptation. Additionally, fascia thickness significantly increased in the LLpBFR group, potentially due to BFR-induced hypoxia, which could have stimulated HIF-1alpha and contributed to increased collagen synthesis. Moreover, BFR had been previously shown to significantly increase growth hormone levels, which in turn could have stimulated collagen production and contributed to increased fascia thickness.

4. Muscle strength

The main findings of this study were that both dynamic and isometric elbow flexion strength of TRAD significantly increased from baseline (□9.00kg and □18.90N, respectively, all $p=.000$), both dynamic and isometric knee extension strength of TRAD significantly increased from baseline (□28.00lbs and □77.90N, respectively, all $p=.000$), both dynamic and isometric elbow flexion strength of LLpBFR significantly increased from baseline (□6.88kg, $p=.001$ and □18.75N, $p=.002$ respectively), and both dynamic and isometric knee extension strength of LLpBFR significantly increased from baseline (□41.25lbs, $p=.003$ and □77.37N, $p=.004$, respectively). When comparing between groups, MANOVA statistics showed that the Hotelling's Trace was .323 and $p=.244$

which was more than the significant level at .05, indicating that both resistance training protocols: TRAD and LLpBFR, resulted in similar adaptation in muscle strength after 6-week programs.

This was the *first* study to demonstrated that the novel program that combined half volume of high intensity sets and the other half of low intensity set with blood flow restriction elicited the similar strength gain effects to the training program that consisted exclusively with high intensity sets.

The numbers of previous studies which compared between high intensity resistance training (>70%1RM) and low intensity resistance training (>50%1RM) with blood flow restriction often demonstrated that even the extent of hypertrophic adaptation would be quite similar, but strength gain was inferior to high intensity training.

For example, Clark et al. (2011) compared the effects of two different 4-week leg extension training programs, each performed three times per week. One program used an external load of 80%1RM, while the other used 30%1RM with blood flow restriction. Both training group were instructed to trained 3 sets with repetition to failure strategy. After 4 weeks, knee extension strength, measured with a knee extension dynamometer at knee joint 60°, significantly increased □171N in the high intensity group and □70N in the low intensity group. The percentage increase in strength was approximately two times higher in the low intensity group (□8%) compared to the high intensity group (□13%).

Another study finding similar results to Clark's was conducted by Karabulut et al. (2010). The researchers investigated 37 healthy male participants, age between 50-64years, performing leg press and knee extension exercises, comparing between high intensity 80%1RM group and low intensity 20%1RM with blood flow restriction group. In high intensity group, participants performed 3 sets of 8 repetitions while in low intensity group, they performed 3 sets of 30,15,15 repetition. After six weeks of training, both groups demonstrated significant strength gains, as evidenced by 1RM knee extension testing and 1RM leg press (p=.001, d=1.7 and p=.001, d=1.86, respectively). However, statistical analysis revealed that the strength increase in the high intensity group was significantly greater in leg extension compared to the low intensity group (□31.2% vs □19.1%, respectively). Nevertheless, the magnitude of change in leg press were similar (□19.3% vs □20.4%, respectively).

In the same way, Kubo et al. (2006) examined isometric knee extension in healthy young participants, training one leg with low load 20%1RM with blood flow restriction and other leg using high load 80%1RM. The participants performed 4 sets of exercise with 30 seconds rest interval between sets. After 12 week of training, 3 days per week, the results demonstrated that maximal isometric knee extension strength as measured at knee joint 90^{o} increased 16.8% (p<.01) and 7.8% (p=0.2) in high load leg and low load leg, respectively. Moreover, higher extent of strength increase was accompanied by higher muscle activation level that was significantly increased from baseline in high load group after training (□3.2%, p=.031). No significant increase in muscle activation was observed in low load group (p=.457). Besides, they also measured tendon stiffness as well and found that only in high load leg that tendon stiffness significantly increased (from 45.6N/mm to 59.3N/mm, or □30%, p<.05) but not in low load leg (from 45.1N/mm to 49.3N/mm, or □9.3%, p>.05). From these findings, results were clearly that Kubo and team demonstrated the superiority of high load training effect on strength adaptation.

Additionally, Libardi et al. (2015) investigated the effect of concurrent training combining between bilateral leg press training and cardiovascular training and measuring on dynamic leg press strength. Eighteen older adults were recruited to the study and randomly assigned to high intensity 70-80%1RM group and low intensity 20-40%1RM group with blood flow restriction. The high intensity group trained for 4 sets of 10 repetitions while the low intensity group employed 4 sets of 30,15,15,15 repetition schemes; besides, both groups performed endurance training for 30-40minutes per day at 50-80%VO_{2peak}. After 12-week programs, the results demonstrated that both 1RM leg press increased up to 38.1% and 35.4%, respectively.

The findings that low intensity with blood flow restriction even could increase muscle strength but still was inferior to high intensity training was supported also by Lixandrao et al. (2015). The searchers compared the effects of different protocols of blood-flow restriction training with different occlusion pressures and intensities on muscle strength. Thirty-five healthy young participants were randomly assigned to one of five groups: BFRRT20/40, BFRRT20/80, BFRRT40/40, BFRRT40/80, and RT80. In BFR group, the first number indicated intensity such as 20%1RM or 40%1RM and the second number indicated occlusion pressure such as 40% or 80%. Training programs was designed for 12 weeks, 2 sessions per week, using knee extension exercise. BFR group trained for 2-3 sets of 15 repetitions while RT80 group trained at 80%1RM for 2-3 sets of 10 repetitions. The results demonstrated that in BFR protocol, no matter what intensity or occlusion pressure utilized, strength increase in BFR conditions was suboptimal compared to high intensity training. The 1RM dynamic knee extension strength increased for 10.3%, 13.2%, 12.1%, and 12.6%, respectively in BFR condition. In contrast, 1RM strength significantly increased up to 21.6% in high intensity group.

The results of this current study demonstrated that both dynamic and isometric strength significantly increased to the similar extents between TRAD and LLpBFR which was interesting because the previous study conducted by Martin-Hernandez and team demonstrated that both dynamic and isokinetic strength substantially increased to the higher extent in high intensity training condition than low intensity with blood flow restriction.

Martin-Hernandez et al. (2012) examined strength adaptations after two different volumes of blood flow restricted programs. They recruited 39 healthy young male university students and randomly assigned to low intensity (20%1RM) low volume with blood flow restriction group (BFR LV) or low intensity high volume with blood flow restriction group (BFR HV) and traditional high intensity (85%1RM) training group. Training protocols lasted 5 weeks, 2 days per week. The BFR LV group performed 4 sets of 30,15,15,15 repetition scheme with 1 minute rest while the BFR HV group doubled the volume of BFR LV (total 8 sets). In contrast, high intensity group performed 3 sets of 8 reps with 1 minute rest. The researcher tested both dynamic 1RM knee extension strength and isokinetic knee extension strength. The findings demonstrated that 1RM strength increased from 142.2kg to 152.2kg (□7.03%, d=0.48), from 138kg to 146.7kg (□6.3%, d=.029), and from 147.9kg to 175kg (□18.32% d=1.19) in BFR LV, BFR HV, and high intensity group, respectively. Moreover, in isokinetic strength test, knee extension strength at 60^{o}/s was increased from 222.4N to 232.8N (□4.68%, d=.032), from 211.9N to 217.5N(□2.64%, d=.018), and from 228.1N to 243N (□6.53%, d=.045), respectively. This study suggested the potential benefits of low volume blood flow restriction training that doubling the volume might not be necessary to induce strength gain.

However, the results of finding in upper body strength was scare. Ozaki et al. (2013) investigated the effects of high intensity resistance training (75%1RM) and low-intensity (30%1RM) blood flow-restricted resistance training on upper body strength measured via bench press exercise. They recruited 19 healthy participants and randomly assigned them to one of two group. High intensity group trained for 3 sets of 10 repetitions while low intensity group trained with 4 sets of 30,15,15,15 repetitions scheme. Training was conducted 3 days per weeks for 6 weeks. After training the findings demonstrated that, bench press strength increased from 47.5kg to 55.9kg (□17.68%) in high intensity group and from 49.3kg to 53.6kg (□8.72%) in low intensity with blood flow restriction group. Unfortunately, they did not investigate the increase in elbow flexion strength; therefore, direct comparison was limited here.

Another study investigating the effect of blood flow restriction training on upper muscle strength was conducted by Thiebaud et al. (2013). Sixteen postmenopausal participants were recruited and randomly assigned to moderate intensity training and low intensity training with blood flow restriction, but this study utilized elastic bands as an external load. The moderate intensity group trained 3 sets of 10 repetitions by adding additional bands until participants report RPE of 7-9 OMNI-RES scale which technically had been suggested to correspond to exercise intensity levels ranging from 70% to 90%1RM while the low intensity group trained with light band of 3 sets of 30,15,15 repetitions scheme. The exercises included seated chest press, seated row, seated shoulder press and the results demonstrated that 1RM strength significantly increase in bench press from about 20% in high intensity group and about 10% in low intensity group.

The significant difference between groups about muscle strength gain would be more obvious if looking into the existing literatures that compared high intensity training and low intensity training without supplementation of blood flow restriction.

For example, Au et al. (2017) recruited forty-six healthy participants and randomly assigned them to a whole-body training program consisting of 3 sets of 8-12 repetitions (high load-low rep) or 3 sets of 20-25 repetitions (low load-high rep) to volitional failure. Muscle strength was measured via 1RM leg press and 1RM bench press exercises. After 12 week of training programs, the results demonstrated that both groups significantly increase fat free mass about 1-2% from baseline (*p*<.01); however, high load-low rep group significantly increased muscle strength of both 1RM bench press and 1RM leg press to higher percentages (□14.14% and □41.90%, respectively) compared to low load-high rep group (□8% and □29.40%, respectively).

Another clear example when comparing between high intensity resistance training and low intensity resistance training programs was the study of Campos et al. (2002). The researcher recruited 27 healthy young male participants and randomly assigned them into one of three groups: Low reps, Inter reps, and High reps. The Low reps group performed 4 sets of very heavy external loads for 3-5 repetitions maximum with 3 min rest, the Int reps 3 sets of moderate external loads for 9-11 repetition maximum with 2 min rest, and finally the High reps performed 20-28 repetition maximum for 2 sets with low external load with 1 min rest. Participants trained for total 8 weeks, 2 days per week for the first 4 weeks and 3 days per week for the final 4 weeks. The exercises performed were leg press, knee extension, and squat. The results demonstrated that 1RM squat, leg extension, and leg press gains were superior at post intervention in Low reps group compared to other groups. For example, 1RM leg press exercise increased significantly about 61% in Low reps compared to only 36% in Inter reps and 32% in High reps. The increases in 1RM strength were accompanied by about 25% and 22.9% increases in type lla and llb fibers cross-sectional area, respectively in Low reps. The extent of increases in fibers area were higher than those of Inter reps (16.27% and 6.46% in type lla and llb, respectively) and High reps (7.97% and 13.52% in type lla and llb, respectively).

It was not only in the lower musculature that the strength adaptation tended to favor high intensity training, in the upper muscle such as bench press strength the previous study showed that significantly greater increases in strength in the high load than low load group. Ogasawa et al. (2013) instructed participants to performed free weight bench press for 3 times per week for 6 weeks. One group of participants trained with high intensity 75%1RM for 3 sets of 10 repetitions while the other group trained with low intensity 30%1RM 3 sets to volitional failure. Muscle strength was measured via 1RM bench press and maximal isometric elbow extension. The results demonstrated that 1RM strength and isometric strength significantly increased ($p<.05$) in both protocols. However, the percent increases in strength were greater in high intensity group (□21% and □13.9% for 1RM and isometric strength, respectively) compared to low intensity group (□8.6% and □6.5% for 1RM and isometric strength, respectively). This indicated that if the goal was to maximized upper body strength, although low intensity to failure protocol was giving promising results but it was still yet suboptimal.

Mechanistically, there was evidence in a previous study which showed that even when lifting with a light load, maximal strength increased, but the neural adaptation was suboptimal compared to heavy load lifting. Jenkins et al. (2017) investigated the effects of heavy load lifting and light load lifting on neural and strength adaptation and found that even when lifting at 30% 1RM, participants increased maximal strength after 6 weeks of training. However, distinct neural adaptations only occurred in the heavy lifting group, where voluntary activation and EMG amplitude were reduced during submaximal torque production as a result of training at 80% 1RM, but not at 30% 1RM. Moreover, lifting a heavy load at 80% 1RM resulted in a significant decrease in neural cost, referring to lower activation required to produce the same absolute torque, to produce the same relative submaximal torques after training, whereas training at 30% 1RM did not. The data suggested that lifting a heavy load might enhance neural efficiency, leading to more effective strength gains and improved performance outcomes.

Additionally, a study conducted by Schoenfeld et al. (2014) investigated muscle activation during leg press exercise at high and low loads in well-trained male participants. The high load was set at 75%1RM and the low load at 30%1RM. Both protocols were designed to continue until failure, with muscle activation monitored via surface EMG. The results indicated that failure occurred after approximately 14 repetitions for the high load and about 45 repetitions for the low load. Notably, muscle activation was significantly higher during the high load protocol compared to the low load, even at the point of muscle failure (mean peak muscle activation 177.3 vs 137.37, $p<.01$, respectively). This suggests that training with a low load of 30% 1RM, despite reaching muscular failure, might not fully activate all muscle fibers. Consequently, this could lead to suboptimal muscle strength adaptation, as the stronger type II fibers, which were typically recruited last, may not be sufficiently engaged.

Taken all together, it could be concluded that even low intensity resistance training (<50% 1RM) could increase either maximal dynamic or isometric strength, though the improvement was not as substantial as with high intensity resistance training (>70% 1RM). Blood flow restriction supplementation has been shown in numerous studies to enhance the hypertrophic response of low intensity resistance training to a level comparable to high intensity training. However, the ability to induce maximal strength gains remained inferior to high intensity training alone. This study was the *first* to address the limitation of low intensity resistance training with blood flow restriction by incorporating some high intensity sets into the program.

The study demonstrated that dividing the total volume into half high intensity and half low intensity sets maximized maximal strength gains, comparable to high intensity training alone. In the other way around, this suggested that exclusively high load training *might not be necessary* to achieve maximal strength gains. The findings showed that both dynamic and isometric strength gains were similar between groups for both upper and lower musculature. When it was possible to reduce external load to manage recovery or reduce the risk of injury, it was highly beneficial to do so. As suggested by Scotts (2014), the potential negative effects of high overall training loads could accumulate over time, impacting athletes during extended training periods. Utilizing BFR strategies to manage training stress was valuable because it reduced external load on the internal system while maintaining training efficacy. Therefore, this presents an opportunity for athletes and trainers to optimize training regimens by incorporating blood flow restriction techniques. By strategically balancing high intensity and low intensity sets, athletes could achieve maximal strength gains while minimizing the risk of injury and managing recovery more effectively. This approach not only enhanced performance but also ensured long-term sustainability and health in athletic training programs.

Moreover, the study provided interesting findings regarding the strength: body weight ratio. Initially, at baseline, the isometric knee extension strength ratio was measured at 3.34 N/kg for TRAD and 3.57 N/kg for LLpBFR. Comparisons with previous systematic reviews, which indicated that healthy adults typically exhibited isometric knee extension forces ranging from 2.92 to 3.45 N/kg at knee extension angles of 50-70 degrees (Sarabon et al., 2021), revealed that our findings closely aligned with these established averages. This supported existing literature on strength ratios in healthy adults. Additionally, research findings indicated that optimal knee extension force production occurred at angles around 60-70 degrees (Kukic et al., 2022), which coincided with our study's testing protocol. Furthermore, after just six weeks of training, both the TRAD and LLpBFR groups demonstrated significant increases in their knee extension strength ratios, reaching 4.47 N/kg and 4.70 N/kg, respectively. This highlighted how progressive strength training just for 6 weeks could notably enhance muscle strength in healthy adult males, exceeding average benchmarks.

Lastly, this study revealed that at baseline, peak isometric elbow flexion strength was 43.90N for the TRAD group and 48.63N for the LLpBFR group. Interestingly, these values were lower than the average elbow flexion strength reported in a previous systematic review. Kotte et al. (2018) found that the average isometric elbow flexion strength in healthy young males across 19 studies was 76.7±15.0N. Our results for both groups in this study fell below this average. This was despite the tests being conducted with the elbow flexed at 90°, an angle reported to produce maximum elbow flexion force (Guenzkofer et al., 2011). Moreover, the average strength: body weight ratio for elbow flexion was 0.65 N/kg in the TRAD group and 0.73 N/kg in the LLpBFR group which was far less than the ratio found in knee extension strength. However, after six weeks of progressive training, the average elbow flexion force increased significantly to 62.80N in the TRAD group and 67.30N in the LLpBFR group. These improvements approached closely the average values reported in Guenzkofer's study. Thus, this study confirmed the effectiveness of a six-week training program in significantly enhancing biceps brachii strength, bringing the values close to the average baseline.

Summary

Both training programs were effective in eliciting muscle strength gains. This study is the first to demonstrate that practitioners may not need to train with high intensity in every set to maximize strength improvements. Incorporating some sets with low intensity and blood flow restriction may benefit muscle joint and tension stress management. High-intensity training increases muscle strength primarily through enhanced neural efficiency and increased motor unit recruitment. While low-intensity training alone can be effective for muscle strength gains, it may not fully stimulate these mechanisms. Therefore, although training with high intensity in every set is not necessary, including some high-intensity sets remains essential for achieving maximal strength gains.

5. Ankle-Brachial Index

The main findings of this study were that the significant change in Ankle-brachial index (ABI) was not observed in either TRAD and LLpBFR group. The pre-intervention ABI ratios of TRAD and LLpBFR were 1.09 and 1.17, respectively. And the post-intervention ABI ratios were 1.08 and 1.12, respectively (□0.02 and □0.05, respectively, all p>.05). MANOVA statistics showed that the Hotelling's Trace was .323 and p=.244, indicating that both resistance training protocols: TRAD and LLpBFR, resulted in similar effect on ABI after 6-week programs.

The finding of this current study added up to the existing literature that both resistance training program with high intensity, 70%1RM and program with low intensity, 30%1RM), plus with blood flow restriction technique were not affecting the ABI ratio. Moreover, this was the first study to investigate the effect of combined intensities protocols on ABI ratio.

In previous study, it was concerned that high intensity resistance training would impair vascular function by increasing arterial stiffness and possibly caused long-term effects as showed in the previous studies. For example, central arterial compliance was reported to decrease by 19% and arterial stiffness significantly increased by 21% after 16-week full-body program with high intensity 80%1RM (Miyachi et al. 2018). In the same way, Tagawa et al. (2018) found that after short duration of 4 weeks of biceps curl exercise, 75%1RM, the carotid arterial compliance also decreased by 13%. Moreover, Collier et al. (2008) found that even at the intensity just 65%1RM, after 4 weeks of training, peripheral muscular arterial stiffness increased by 8.7%.

Although this study did not directly assess arterial stiffness, this study referred to ABI ratio in indirectly investigating the arterial function and risk of peripheral arterial disease. Generally, the ratio of ABI at under 0.9 was considered to be at risk of vascular dysfunction and risky of peripheral arterial disease (Xu et al. 2013) or atherosclerosis in lower limb (Casey et al. 2019), while an ABI ratio higher than 1.4 suggests a noncompressible calcified vessel (McClary & Massey 2023). Both too low, <0.9, and too high, >1.4, value was life-threatening and needed of medical consultation and must be referred to vascular specialist (Rac-Albu et al. 2014).

The results of this study agree with previous studies which found that resistance training program combined with blood flow restriction was safe, not affecting ABI ratio after perioid of training. For example, Clark et al. (2011) investigated the effect of knee extension exercise as used in this study with 16 young healthy male and female participants. Participants either performed knee extension at 80%1RM or 30%1RM with blood flow restriction and the results demonstrated that the ABI ratios in 80%1RM group changed from 1.15 to 1.09 and blood flow restriction group changed from 1.08 to 1.07, with no significant difference from baseline in both groups.

It was worth highlighting again that ABI ratio was the value in range not specific number, meaning that the value from above 0.9 to 1.4 was consider acceptable in medical condition (Casey et al. 2019). The ABI was calculated from highest pressure of lower leg divided by the highest pressure of upper arm (Aboyans et al. 2012). Therefore, the ratio within these range was still safe and not problematic.

Generally speaking, ankle blood pressure is normally higher than arm blood pressure. Gong et al. (2015) investigated the normal range of ankle systolic pressure in healthy subjects with normal arm systolic pressure. They found that the ankle systolic blood pressure was significantly higher than the arm systolic blood pressure (right ankle 137.1±16.9 vs right arm 119.7±11.4 mmHg, $p<0.05$). Based on the 99% method, the normal range of ankle systolic pressure was about 94-181mmHg for the total population, with specifically the young (18-44years) range being about 84-166mmHg.

In previous study, Yasuda et al. (2014) found that when a group of healthy older adults performing leg press and knee extension exercises with intensity 20-30%1RM with blood flow restriction, after 12-week training program, ABI ratio was not significantly affected (1.13 to 1.15, from pre to post intervention, respectively). In the same way, when upper body muscles were trained, the ABI ratio was not affected as well. Yasuda et al. (2015) investigated the effect of elastic band training with blood flow restriction, performing arm curl and triceps pushdown exercises, in elderly women. They found that the ABI ratio was from 1.17 at pre intervention to 1.14 at post intervention.

Moreover, Yasuda et al. (2016) examined the effect of two elastic band intensities with BFR on vascular function in older women. The protocols separated the training group into low intensity with BFR and moderate to high intensity. Both groups performed squat and knee extension exercises, twice per week for 12 weeks. Intensity was changed by adding up the band, the moderate to high intensity group using 2 gold bands and 1 gold band, while the low intensity with BFR group, they use only 1 gold band. Finding demonstrated that although the band was twice the resistance level in moderate to heavy group, ABI was not affected in both groups (1.14 to 1.15, in low intensity group and 1.11 to 1.11 in high intensity group. This was supported by this study that either TRAD or LLpBFR was not negatively affect the change of ABI ratio (□0.02, p=.555 and □0.05, p=.482, respectively).

In a particular group of the population, such as patients with type 2 diabetes, Gibbs et al. (2013) investigated the effect of resistance training combined with aerobic training on the ankle-brachial index (ABI). Seventy participants were instructed to perform lat pull-downs, leg extensions, leg curls, bench presses, leg presses, shoulder presses, and seated mid-rowing exercises, completing 2 sets of each at 12-15 repetitions at 50% 1RM. This was combined with aerobic exercise at a target heart rate between 60–90% of maximum heart rate for 45 minutes, for 3 sessions per week. After 26 weeks of training, they found that the ABI ratio improved from 1.02±0.01 at baseline to 1.07±0.002. This change in ABI was accompanied by a significant correlation with decreased HbA1c levels, systolic blood pressure, and diastolic blood pressure, indicating an overall improvement in cardiovascular health and glycemic control. These findings suggested that a combination of resistance and aerobic training could be beneficial in managing type 2 diabetes and improving vascular function.

It was worth mentioning that the LLpBFR in this current study also had a more aerobic nature in its program design due to the high number of repetitions at low intensity (30% 1RM) and longer time under tension per set compared to heavy sets TRAD. A recent study by Mang et al. (2022) proposed that resistance training could yield positive adaptations in aerobic fitness, such as improved muscle capillarization and increased mitochondrial adaptations. The study suggested that a program design characterized by performing 20-35 repetitions per set with 30-50% 1RM and a time under tension of about 60-105 seconds would optimize aerobic adaptation, partly due to greater metabolic stress (Mang et al., 2022). Although the current study did not measure time under tension per set, the number of repetitions performed in each set of low-intensity with practical blood flow restriction perfectly fell within, or even beyond, this recommended range. As mentioned earlier, the number of repetitions performed during low-intensity sets of preacher curls were 23.5 reps, 24 reps, 28 reps, 29.2 reps, 35.5 reps, and 36 reps from weeks 1-6, respectively, and the number of repetitions performed during low-intensity sets of knee extensions were 32.9 reps, 40.3 reps, 42.0 reps, 44.5

reps, 49.8 reps, and 51.9 reps from weeks 1-6, respectively. Therefore, it was possible that these high repetition, low-intensity exercises with blood flow restriction contributed to improved aerobic capacity and overall fitness.

Collectively, the results of this study and the existing literature suggested that both high-intensity (70% 1RM) and low-intensity (30% 1RM) resistance training combined with blood flow restriction did not negatively impact the ankle-brachial index in healthy subjects, regardless of the age, indicating the safety of these training modalities for vascular health. Additionally, previous research, such as that by Gibbs’. highlighted that combining resistance and aerobic training could improve cardiovascular markers, supporting the potential benefits of multifaceted training programs for enhancing overall cardiovascular and metabolic health.

Summary

Both training programs did not affect the ankle-brachial index, suggesting that both high-intensity training alone and high-intensity training combined with low-intensity training and blood flow restriction are safe for enhancing muscle strength and hypertrophy. However, incorporating high-repetition low-intensity training into the program may offer slight benefits for cardiovascular adaptation in the long term, especially if the sets consist of approximately 20-35 repetitions with a time under tension of around 60-105 seconds.

6. Rate of perceived exertion

In this study, the rate of perceived exertion was measured using the OMNI-RES scale at the end of each weekly training session for all participants. Participants were asked to rate "how hard or heavy they felt the session was on a scale from 1 to 10, with 10 being the most difficult or hardest." The findings were noteworthy. Notably, during the first two weeks, the RPE for LLpBFR group was significantly lower compared to TRAD group, with scores of 6.75 versus 7.80 (p=.010) in the first week and 6.88 versus

8.20 (*p*=.000) in the second week. However, in the subsequent four weeks, the LLpBFR group reported perception scores similar to those of the TRAD group. Trend analysis revealed a gradual increase in rate of perceived exertion for the LLpBFR group over time, whereas the TRAD group maintained a consistently high rate of perceived exertion throughout the duration of the program, indicating a consistently challenging level of exertion from the start to the end of the program.

In past research, the OMNI-RES scale was frequently used to assess participants' subjective perceptions of training intensity. For instance, in a study by Robertson et al. (2003), the OMNI-RES scale was utilized with young healthy participants aged 18 to 30 years. The participants were instructed to perform three sets of 4, 8, and 12 repetitions of both biceps curl and knee extension at 65% of their one-repetition maximum. It was found that the OMNI-RES scores increased linearly with the number of repetitions performed for both exercises. Specifically, for the biceps curl and knee extension at 4 repetitions at 65%1RM, the OMNI-RES scores were approximately 4 and 5, respectively. At 8 repetitions, the scores were found to increase to around 6 for the biceps curl and 8 for the knee extension, while at 12 repetitions, the scores were about 8.5 and 9.5, respectively. This demonstrated that the OMNI-RES scale effectively represented how hard the participants perceived the exertion after training.

While OMNI-RES score might be implemented after every set of training, it could also be implemented as the session perception of exertion, such as conducted in this current study, as well. For example, McGuigan et al. (2008) investigate the use of the OMNI-RES to monitor training intensity of different modes of resistance exercise in overweight or obese children. They recruit 61 children, average age of 9.7 years, to perform resistance training, 3 sessions per week for 4 weeks. Every day of training would consist of different 8 exercises. After each session, these children were asked for "how was the workout" and rating from 0 to 10. They found that the average session OMNI-RES score was 3.1 which indicated "somewhat easy" for these children.

In this current study, the OMNI-RES score on average of 6 weeks was 8.3 and 8 in TRAD and LLpBFR, respectively. The number was surely higher compared to children's program of McGuigan's study, maybe partly because of the external load use.

Another study that employed OMNI-RES score was conducted by Aniceto et al. (2015). They did the interesting study by compared two training protocols with the same group of 10 healthy male participants. In the first experiment, these men performed 3 sets at 60%1RM of 8 exercises including bench press, leg press, seated row, leg curl, triceps pulley, leg extension, biceps curl, and adductor chair, that counts in total 24 sets per session with 1 minute rest between set. After 5-7days, the second experiment was that the same group of men performed 8 exercises in circuit fashion such as from first set of bench press to first set of leg press to first set of seated row and so on. They were instructed to repeat for 3 rounds. In every 3 sets of exercising, they were asked to rate OMNI-RES score from 0 to 10. The results demonstrated that the OMNI-RES score was higher in multiple set training fashion compared to circuit fashion. It was possible that because of the style characteristics of multiple set fashion requiring subsequent sets performed by the same muscle group, there might be greater fatigue accumulation and production of muscle lactate and less removal, finally resulting in higher OMNI-RES scores.

Mechanistically, this was supported by previous studies showing that there were the links between perceived exertion scores and increases in select physiological variables, such as lactic acid concentration and muscle activity. For example, Zinoubi et al. (2018) demonstrated a parallel rise in blood lactate, heart rate, and perceived exertion during cycling at 160W and 240W. At 160W, with a perceived exertion score of 12, blood lactate was 5.2 mmol/L and heart rate was 148 bpm. At a score of 13.4, blood lactate rose to 6.7 mmol/L and heart rate to 152 bpm. Similarly, at 240W, with a perceived exertion score of 12.7 on the Borg scale, blood lactate increased to 6.5 mmol/L and heart rate to 154 bpm; at a score of 14, blood lactate reached 7.5 mmol/L and heart rate 160 bpm.

Furthermore, Lagally and Robertson (2006) demonstrated a strong linear correlation between the OMNI-RES and Borg RPE scales for both men and women, with validity coefficients ranging from $r = 0.94$ to 0.97. This high construct validity indicated that both scales measured similar properties of exertion and could be used interchangeably. Therefore, despite Zinoubi's use of the Borg scale, the findings were relevant and applicable. Another study conducted by Pierce et al. (1993) found a reduction in blood lactate and heart rate and a corresponding reduction in Borg scale RPE after 12 weeks of squat training when comparisons were made using an absolute load. The researcher tested participants by letting them squatting for 7 sets. The intensities gradually increased from 45%1RM in first set and 55%1RM in the second set and 62.5%1RM for the rest 5 sets. Each set was performed for 10 repetitions. The finding demonstrated that the Pre, after 7 sets of squat testing, the peak blood lactate was 11.9mmol/L and after 8 weeks of strength training program, the peak blood lactate decreased to 5.1mmol/L, as well as rate of perceived exertion scores that significantly decreased after reporting every set of squatting compared to at Pre. Moreover, peak heart rate was also reduced from 185bpm at Pre to 161bpm after 8 weeks of training.

Summary

The current study demonstrated that both TRAD group and LLpBFR group significantly increased muscle thickness and area of both biceps brachii and vastus lateralis. Additionally, the preferable muscle architectural adaptations of vastus lateralis were similar between the two protocols. Moreover, both dynamic and isometric muscle strength also significantly improved after 6 weeks of training. Importantly, neither training method negatively impacted ankle-brachial index scores. Interestingly, during the first and second weeks, the OMNI-RES scores were significantly lower in the LLpBFR group, suggesting that LLpBFR program may be a more psychologically friendly training program. For individuals who have difficulty tolerating high levels of pain or exertion, a resistance training program that gradually increases in psychological difficulty can be highly beneficial (Williams et al., 2008). This approach can help individuals avoid the intense discomfort of initial training sessions, potentially improving adherence and fostering long-term participation and commitment, thereby reducing negative associations with resistance training (Rhodes et al., 2017).

Limitation

This study has several limitations that should be considered. The use of practical blood flow restriction, reliant on subjective perception, may not have ensured completely accurate pressure; future research should use clinically pressurized cuffs to better evaluate outcomes related to hypertrophy, strength, and vascular function. Additionally, the results are limited to healthy young male participants, so the applicability to other genders and age groups, such as females and the elderly, may not be straightforward. Moreover, the study also focused solely on the preacher curl and knee extension machines, which limits the generalizability of the findings to other muscle groups; further research should include additional muscles, such as the hamstrings or triceps. Lastly, since the participants were untrained and likely more responsive to training stimuli, future studies should involve experienced lifters to assess the protocol's effectiveness in a more seasoned population.

Practical implications of this study

Hypertrophy Outcomes: Resistance training practitioners can anticipate positive hypertrophic adaptations using either TRAD or LLpBFR protocols based on this study's findings.

Interchangeable Protocols: TRAD and LLpBFR can be used interchangeably or programmed alternately, offering flexibility in resistance training regimens.

Strength Gains with Low Intensity: Muscle strength gains can be achieved without consistently training at high intensity. This study demonstrates that LLpBFR, which involves low-intensity training for a portion of the volume, effectively induces strength gains comparable to those achieved with TRAD.

Practical Blood Flow Restriction: Practical blood flow restriction in LLpBFR group appears to be a viable option for those who can not access to pneumatic cuffs and still effective to elicit hypertrophic and strength gain outcome, comparable to TRAD.

Safety: Both TRAD and LLpBFR protocols are safe concerning vascular health, making them viable options for resistance training programs.

Future recommendation

Future research should explore the effects of TRAD and LLpBFR protocols, of this study, on other muscle groups such as biceps femoris or triceps brachii to provide more comprehensive information on the effectiveness of these program designs. Additionally, studies should include diverse populations, such as female participants, younger individuals, and older adults, to enhance the generalizability of the findings. Implementing advanced imaging techniques like MRI and ultrasound to corroborate the results from similar studies is further recommended to obtain precise data.

Appendix

Appendix A: Instruments and training

ISOFORCE MACHINE

(ISOFORCE, GERMANY)

BLOOD FLOW RESTRICTION

PNEUMATIC CUFFS (H+CUFF , USA)

HANDHELD VASCULAR DOPPLE

ELASTIC WRAPS

(GRIZZLY FITNESS, CANADA)

PREACHER CURL MACHINE (BODY-SOLID,USA)

KNEE EXTENSION MACHINE (BODY-SOLID,USA)

TRAINING

KNEE EXTENSION

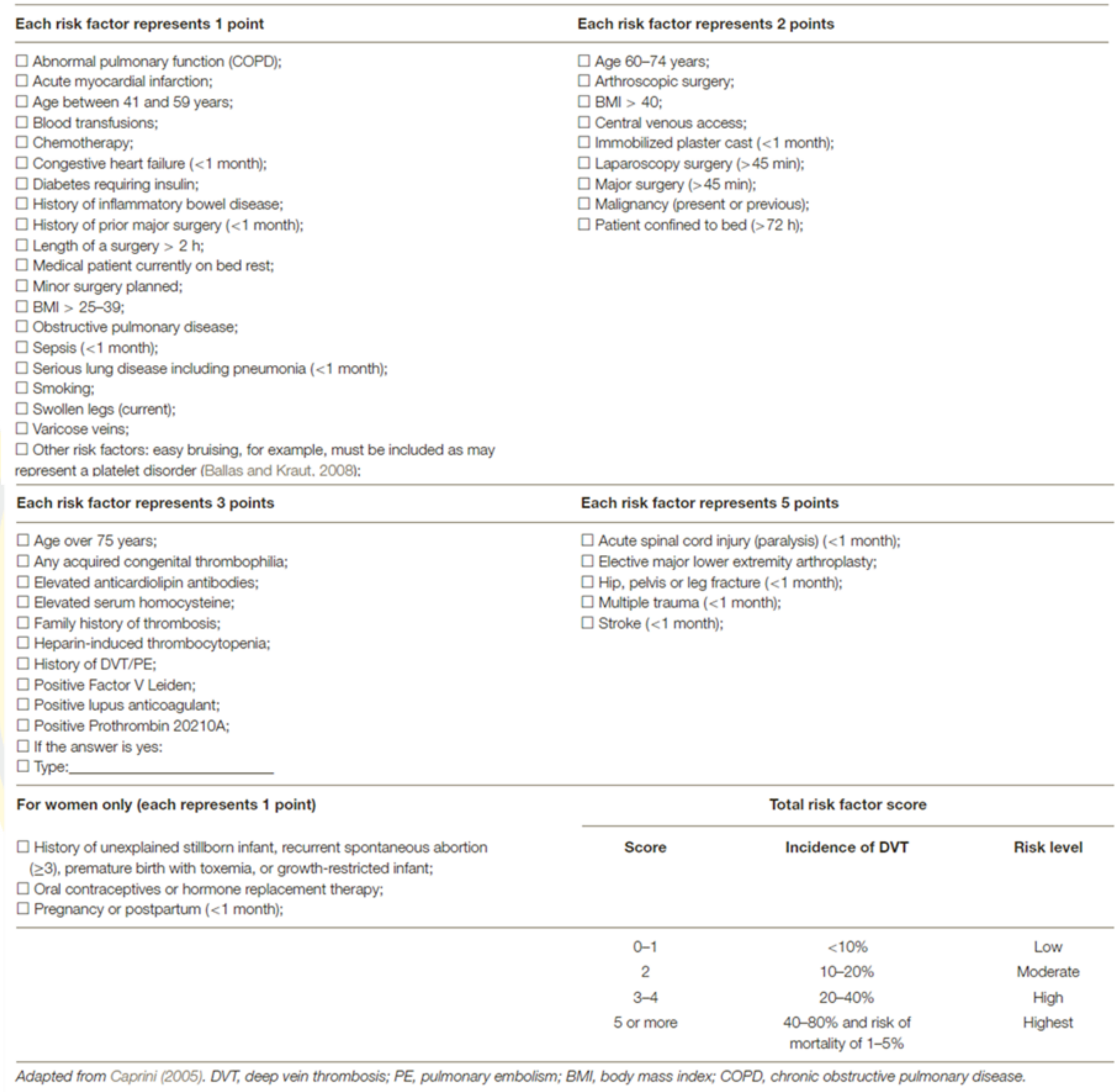
TRAINING

PREACHER CUR

ISOMETRIC ELBOW FLEXION TEST

ISOMETRIC KNEE EXTENSION TEST

Appendix B: Risk assessment form



Each risk factor represents 1 point

☐ Abnormal pulmonary function (COPD);
☐ Acute myocardial infarction;
☐ Age between 41 and 59 years;
☐ Blood transfusions;
☐ Chemotherapy;
☐ Congestive heart failure (<1 month);
☐ Diabetes requiring insulin;
☐ History of inflammatory bowel disease;
☐ History of prior major surgery (<1 month);
☐ Length of a surgery > 2 h;
☐ Medical patient currently on bed rest;
☐ Minor surgery planned;
☐ BMI > 25–39;
☐ Obstructive pulmonary disease;
☐ Sepsis (<1 month);
☐ Serious lung disease including pneumonia (<1 month);
☐ Smoking;
☐ Swollen legs (current);
☐ Varicose veins;
☐ Other risk factors: easy bruising, for example, must be included as may represent a platelet disorder (Ballas and Kraut, 2008);

Each risk factor represents 2 points

☐ Age 60–74 years;
☐ Arthroscopic surgery;
☐ BMI > 40;
☐ Central venous access;
☐ Immobilized plaster cast (<1 month);
☐ Laparoscopy surgery (>45 min);
☐ Major surgery (>45 min);
☐ Malignancy (present or previous);
☐ Patient confined to bed (>72 h);

Each risk factor represents 3 points

☐ Age over 75 years;
☐ Any acquired congenital thrombophilia;
☐ Elevated anticardiolipin antibodies;
☐ Elevated serum homocysteine;
☐ Family history of thrombosis;
☐ Heparin-induced thrombocytopenia;
☐ History of DVT/PE;
☐ Positive Factor V Leiden;
☐ Positive lupus anticoagulant;
☐ Positive Prothrombin 20210A;
☐ If the answer is yes:
☐ Type:____________________

Each risk factor represents 5 points

☐ Acute spinal cord injury (paralysis) (<1 month);
☐ Elective major lower extremity arthroplasty;
☐ Hip, pelvis or leg fracture (<1 month);
☐ Multiple trauma (<1 month);
☐ Stroke (<1 month);

For women only (each represents 1 point)

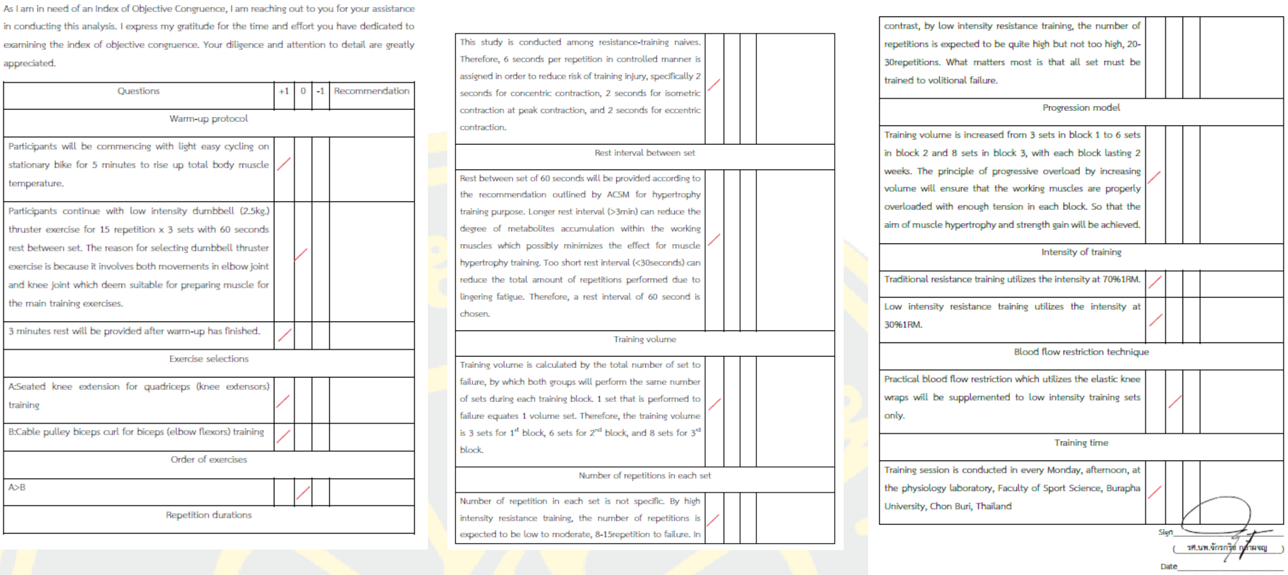
☐ History of unexplained stillborn infant, recurrent spontaneous abortion (≥3), premature birth with toxemia, or growth-restricted infant;
☐ Oral contraceptives or hormone replacement therapy;
☐ Pregnancy or postpartum (<1 month);

Total risk factor score

Score	Incidence of DVT	Risk level
0–1	<10%	Low
2	10–20%	Moderate
3–4	20–40%	High
5 or more	40–80% and risk of mortality of 1–5%	Highest

Adapted from Caprini (2005). DVT, deep vein thrombosis; PE, pulmonary embolism; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

Appendix C: Index of Objective Congruence



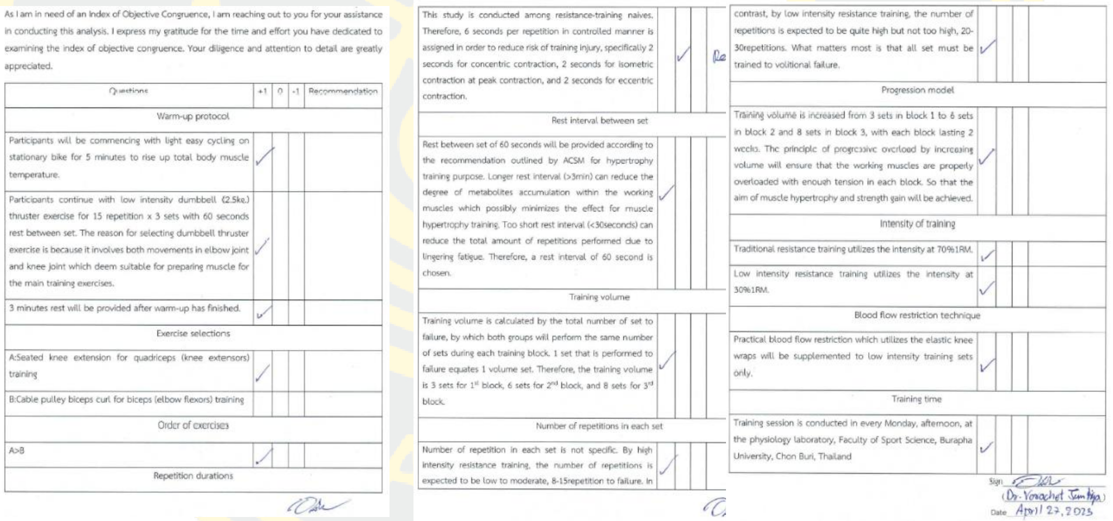
As I am in need of an Index of Objective Congruence, I am reaching out to you for your assistance in conducting this analysis. I express my gratitude for the time and effort you have dedicated to examining the index of objective congruence. Your diligence and attention to detail are greatly appreciated.

Questions	+1	0	-1	Recommendation
Warm-up protocol				
Participants will be commencing with light easy cycling on stationary bike for 5 minutes to rise up total body muscle temperature.	✓			
Participants continue with low intensity dumbbell (2.5kg.) thruster exercise for 15 repetition x 3 sets with 60 seconds rest between set. The reason for selecting dumbbell thruster exercise is because it involves both movements in elbow joint and knee joint which deem suitable for preparing muscle for the main training exercises.		✓		
3 minutes rest will be provided after warm-up has finished.	✓			
Exercise selections				
A:Seated knee extension for quadriceps (knee extensors) training	✓			
B:Cable pulley biceps curl for biceps (elbow flexors) training	✓			
Order of exercises				
A>B		✓		
Repetition durations				
This study is conducted among resistance-training naives. Therefore, 6 seconds per repetition in controlled manner is assigned in order to reduce risk of training injury, specifically 2 seconds for concentric contraction, 2 seconds for isometric contraction at peak contraction, and 2 seconds for eccentric contraction.	✓			
Rest interval between set				
Rest between set of 60 seconds will be provided according to the recommendation outlined by ACSM for hypertrophy training purpose. Longer rest interval (>3min) can reduce the degree of metabolites accumulation within the working muscles which possibly minimizes the effect for muscle hypertrophy training. Too short rest interval (<30seconds) can reduce the total amount of repetitions performed due to lingering fatigue. Therefore, a rest interval of 60 second is chosen.	✓			
Training volume				
Training volume is calculated by the total number of set to failure, by which both groups will perform the same number of sets during each training block. 1 set that is performed to failure equates 1 volume set. Therefore, the training volume is 3 sets for 1st block, 6 sets for 2nd block, and 8 sets for 3rd block.	✓			
Number of repetitions in each set				
Number of repetition in each set is not specific. By high intensity resistance training, the number of repetitions is expected to be low to moderate, 8-15repetition to failure. In contrast, by low intensity resistance training, the number of repetitions is expected to be quite high but not too high, 20-30repetitions. What matters most is that all set must be trained to volitional failure.	✓			
Progression model				
Training volume is increased from 3 sets in block 1 to 6 sets in block 2 and 8 sets in block 3, with each block lasting 2 weeks. The principle of progressive overload by increasing volume will ensure that the working muscles are properly overloaded with enough tension in each block. So that the aim of muscle hypertrophy and strength gain will be achieved.	✓			
Intensity of training				
Traditional resistance training utilizes the intensity at 70%1RM.	✓			
Low intensity resistance training utilizes the intensity at 30%1RM.	✓			
Blood flow restriction technique				
Practical blood flow restriction which utilizes the elastic knee wraps will be supplemented to low intensity training sets only.		✓		
Training time				
Training session is conducted in every Monday, afternoon, at the physiology laboratory, Faculty of Sport Science, Burapha University, Chon Buri, Thailand	✓			

Sign__________

(รศ.นพ.จักรกริช กล้าผจญ)

Date__________



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Questions	+1	0	-1	Recommendation
Warm-up protocol				
Participants will be commencing with light easy cycling on stationary bike for 5 minutes to rise up total body muscle temperature.	✓			
Participants continue with low intensity dumbbell (2.5kg.) thruster exercise for 15 repetition x 3 sets with 60 seconds rest between set. The reason for selecting dumbbell thruster exercise is because it involves both movements in elbow joint and knee joint which deem suitable for preparing muscle for the main training exercises.	✓			
3 minutes rest will be provided after warm-up has finished.	✓			
Exercise selections				
A:Seated knee extension for quadriceps (knee extensors) training	✓			
B:Cable pulley biceps curl for biceps (elbow flexors) training				
Order of exercises				
A>B	✓			
Repetition durations				
This study is conducted among resistance-training naives. Therefore, 6 seconds per repetition in controlled manner is assigned in order to reduce risk of training injury, specifically 2 seconds for concentric contraction, 2 seconds for isometric contraction at peak contraction, and 2 seconds for eccentric contraction.	✓			Re
Rest interval between set				
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Training volume				
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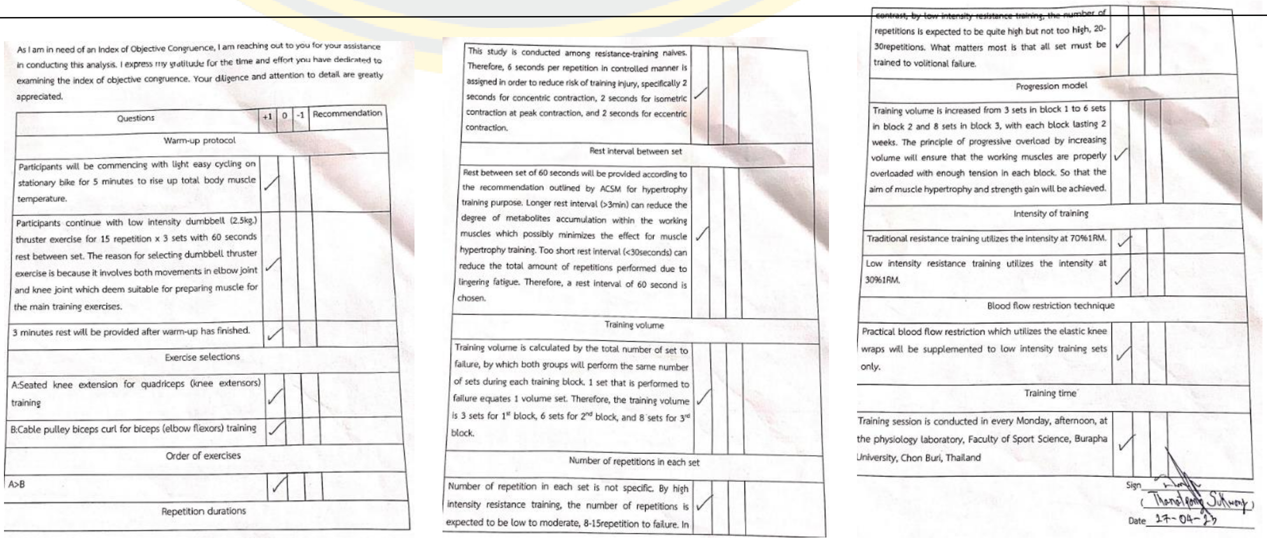
Progression model				
Training volume is increased from 3 sets in block 1 to 6 sets in block 2 and 8 sets in block 3, with each block lasting 2 weeks. The principle of progressive overload by increasing volume will ensure that the working muscles are properly overloaded with enough tension in each block. So that the aim of muscle hypertrophy and strength gain will be achieved.	✓			
Intensity of training				
Traditional resistance training utilizes the intensity at 70%1RM.	✓			
Low intensity resistance training utilizes the intensity at 30%1RM.	✓			
Blood flow restriction technique				
Practical blood flow restriction which utilizes the elastic knee wraps will be supplemented to low intensity training sets only.	✓			
Training time				
Training session is conducted in every Monday, afternoon, at the physiology laboratory, Faculty of Sport Science, Burapha University, Chon Buri, Thailand	✓			

Sign__________

(Dr. Vorachet Jumtiya)

Date April 27, 2023



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Questions	+1	0	-1	Recommendation
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Participants continue with low intensity dumbbell (2.5kg.) thruster exercise for 15 repetition x 3 sets with 60 seconds rest between set. The reason for selecting dumbbell thruster exercise is because it involves both movements in elbow joint and knee joint which deem suitable for preparing muscle for the main training exercises.	✓			
3 minutes rest will be provided after warm-up has finished.	✓			
Exercise selections				
A:Seated knee extension for quadriceps (knee extensors) training	✓			
B:Cable pulley biceps curl for biceps (elbow flexors) training	✓			
Order of exercises				
A>B	✓			
Repetition durations				
This study is conducted among resistance-training naives. Therefore, 6 seconds per repetition in controlled manner is assigned in order to reduce risk of training injury, specifically 2 seconds for concentric contraction, 2 seconds for isometric contraction at peak contraction, and 2 seconds for eccentric contraction.	✓			
Rest interval between set				
Rest between set of 60 seconds will be provided according to the recommendation outlined by ACSM for hypertrophy training purpose. Longer rest interval (>3min) can reduce the degree of metabolites accumulation within the working muscles which possibly minimizes the effect for muscle hypertrophy training. Too short rest interval (<30seconds) can reduce the total amount of repetitions performed due to lingering fatigue. Therefore, a rest interval of 60 second is chosen.	✓			
Training volume				
Training volume is calculated by the total number of set to failure, by which both groups will perform the same number of sets during each training block. 1 set that is performed to failure equates 1 volume set. Therefore, the training volume is 3 sets for 1st block, 6 sets for 2nd block, and 8 sets for 3rd block.	✓			
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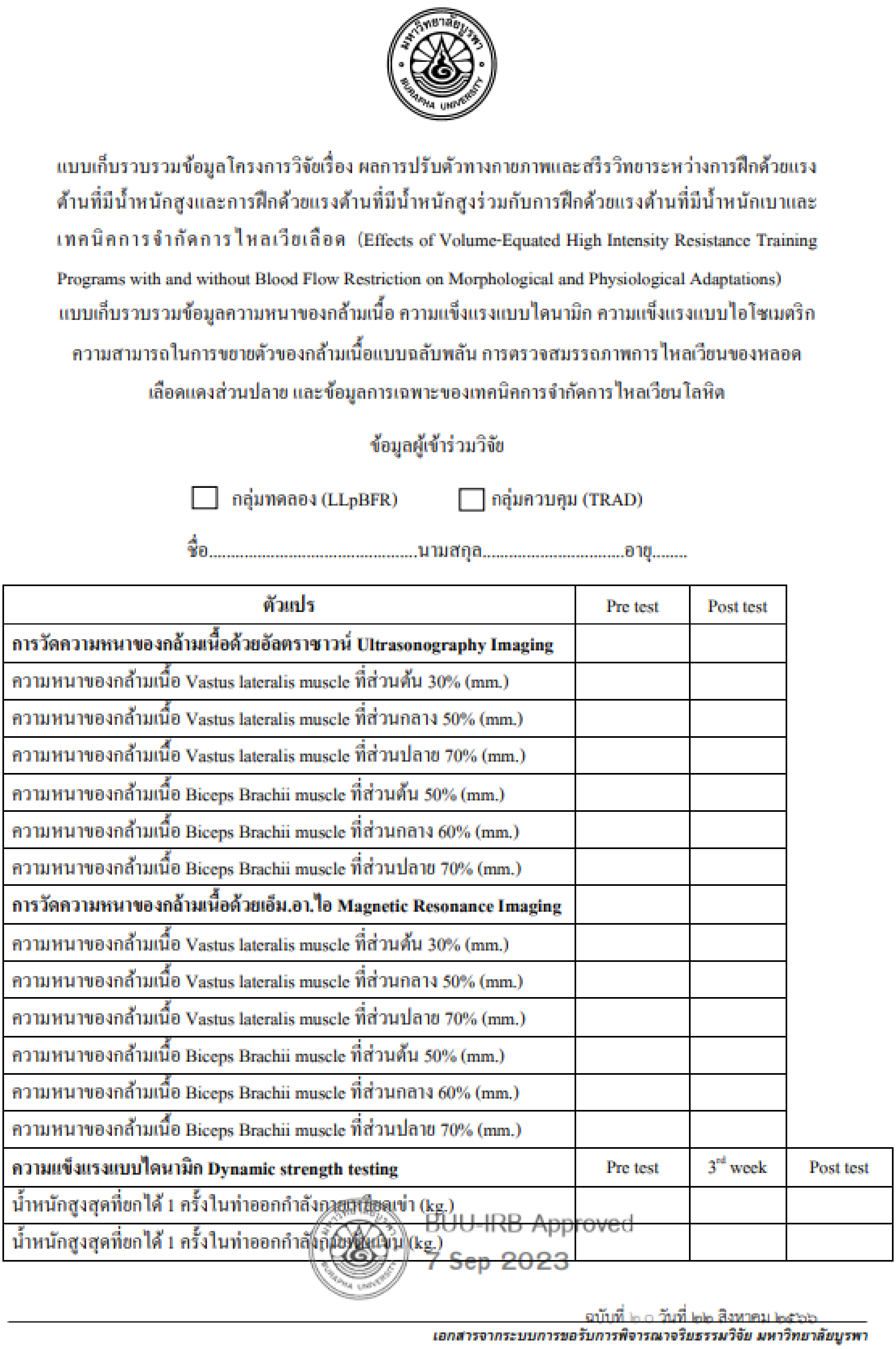
Progression model				
Training volume is increased from 3 sets in block 1 to 6 sets in block 2 and 8 sets in block 3, with each block lasting 2 weeks. The principle of progressive overload by increasing volume will ensure that the working muscles are properly overloaded with enough tension in each block. So that the aim of muscle hypertrophy and strength gain will be achieved.	✓			
Intensity of training				
Traditional resistance training utilizes the intensity at 70%1RM.	✓			
Low intensity resistance training utilizes the intensity at 30%1RM.	✓			
Blood flow restriction technique				
Practical blood flow restriction which utilizes the elastic knee wraps will be supplemented to low intensity training sets only.	✓			
Training time				
Training session is conducted in every Monday, afternoon, at the physiology laboratory, Faculty of Sport Science, Burapha University, Chon Buri, Thailand	✓			

Sign__________

(Thanatpong Sukwong)

Date 17-04-23

Appendix D: Data collection sheet



แบบเก็บรวบรวมข้อมูลโครงการวิจัยเรื่อง ผลการปรับตัวทางกายภาพและสรีรวิทยาระหว่างการฝึกด้วยแรงต้านที่มีน้ำหนักสูงและการฝึกด้วยแรงต้านที่มีน้ำหนักสูงร่วมกับการฝึกด้วยแรงต้านที่มีน้ำหนักเบาและเทคนิคการจำกัดการไหลเวียนเลือด (Effects of Volume-Equated High Intensity Resistance Training Programs with and without Blood Flow Restriction on Morphological and Physiological Adaptations)

แบบเก็บรวบรวมข้อมูลความหนาของกล้ามเนื้อ ความแข็งแรงแบบไดนามิก ความแข็งแรงแบบไอโซเมตริก ความสามารถในการขยายตัวของกล้ามเนื้อแบบฉลับพลัน การตรวจสมรรถภาพการไหลเวียนของหลอดเลือดแดงส่วนปลาย และข้อมูลการเฉพาะของเทคนิคการจำกัดการไหลเวียนโลหิต

ข้อมูลผู้เข้าร่วมวิจัย

☐ กลุ่มทดลอง (LLpBFR) ☐ กลุ่มควบคุม (TRAD)

ชื่อ..นามสกุล...............................อายุ........

ตัวแปร	Pre test	Post test	
การวัดความหนาของกล้ามเนื้อด้วยอัลตราซาวน์ Ultrasonography Imaging			
ความหนาของกล้ามเนื้อ Vastus lateralis muscle ที่ส่วนต้น 30% (mm.)			
ความหนาของกล้ามเนื้อ Vastus lateralis muscle ที่ส่วนกลาง 50% (mm.)			
ความหนาของกล้ามเนื้อ Vastus lateralis muscle ที่ส่วนปลาย 70% (mm.)			
ความหนาของกล้ามเนื้อ Biceps Brachii muscle ที่ส่วนต้น 50% (mm.)			
ความหนาของกล้ามเนื้อ Biceps Brachii muscle ที่ส่วนกลาง 60% (mm.)			
ความหนาของกล้ามเนื้อ Biceps Brachii muscle ที่ส่วนปลาย 70% (mm.)			
การวัดความหนาของกล้ามเนื้อด้วยเอ็ม.อา.ไอ Magnetic Resonance Imaging			
ความหนาของกล้ามเนื้อ Vastus lateralis muscle ที่ส่วนต้น 30% (mm.)			
ความหนาของกล้ามเนื้อ Vastus lateralis muscle ที่ส่วนกลาง 50% (mm.)			
ความหนาของกล้ามเนื้อ Vastus lateralis muscle ที่ส่วนปลาย 70% (mm.)			
ความหนาของกล้ามเนื้อ Biceps Brachii muscle ที่ส่วนต้น 50% (mm.)			
ความหนาของกล้ามเนื้อ Biceps Brachii muscle ที่ส่วนกลาง 60% (mm.)			
ความหนาของกล้ามเนื้อ Biceps Brachii muscle ที่ส่วนปลาย 70% (mm.)			
ความแข็งแรงแบบไดนามิก Dynamic strength testing	Pre test	3rd week	Post test
น้ำหนักสูงสุดที่ยกได้ 1 ครั้งในท่าออกกำลังกายเหยียดเข่า (kg.)			
น้ำหนักสูงสุดที่ยกได้ 1 ครั้งในท่าออกกำลังกายงอแขน (kg.)			

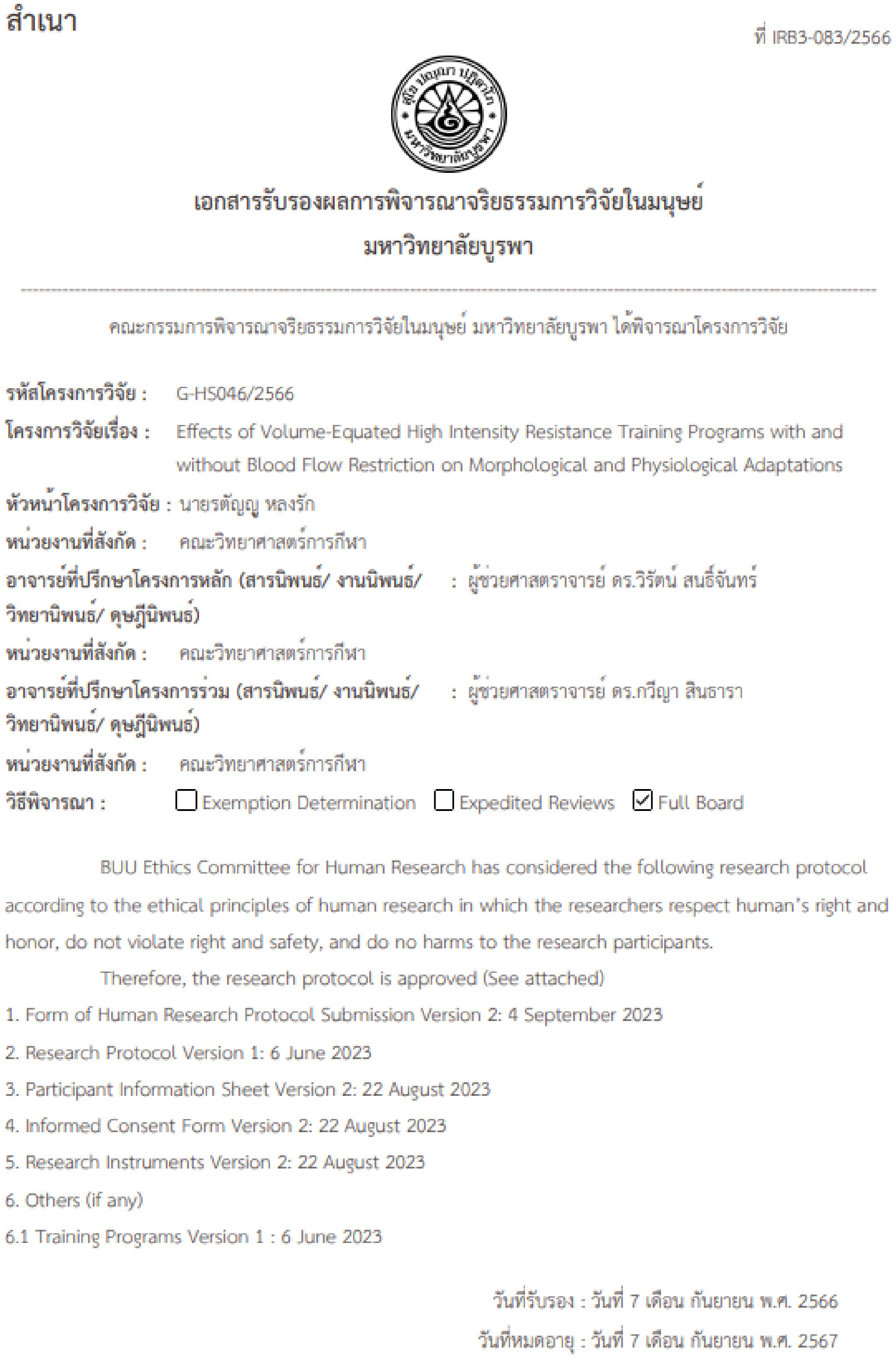
BUU-IRB Approved
7 Sep 2023

ฉบับที่ ๒.๐ วันที่ ๒๒ สิงหาคม ๒๕๖๖

เอกสารจากระบบการขอรับการพิจารณาจริยธรรมวิจัย มหาวิทยาลัยบูรพา

ความแข็งแรงแบบไอโซเมตริก Isometric strength testing			
ความสามารถในการออกแรงสูงสุดที่ทำได้ในท่าเหยียดเข่า (newton)			
ความสามารถในการออกแรงสูงสุดที่ทำได้ในท่าพับแขน (newton)			
ความสามารถในการขยายตัวของกล้ามเนื้อแบบฉลับพลัน Acute exercise-induced metabolic stress	1st week	6th week	
การขยายขนาดฉลับพลันของกล้ามเนื้อขา (mm.)			
การขยายขนาดฉลับพลันของกล้ามเนื้อแขน (mm.)			
การตรวจสมรรถภาพการไหลเวียนของหลอดเลือดแดงส่วนปลาย Peripheral vascular function	Pre test	Post test	
ดัชนีข้อเท้าแขน Ankle-Brachial Index (A.U.)			
ข้อมูลการเฉพาะของเทคนิคการจำกัดการไหลเวียนโลหิต Blood flow restriction details			
100% Arterial occlusion pressure (mmHg)			
40% Arterial occlusion pressure (mmHg)			
ความรู้สึกรับรู้ถึงความยากในการฝึก OMNI-RES			
Session 1 (A.U.)			
Session 2 (A.U.)			
Session 3 (A.U.)			
Session 4 (A.U.)			
Session 5 (A.U.)			
Session 6 (A.U.)			

Appendix E: Ethical approval



สำเนา

ที่ IRB3-083/2566

เอกสารรับรองผลการพิจารณาจริยธรรมการวิจัยในมนุษย์
มหาวิทยาลัยบูรพา

คณะกรรมการพิจารณาจริยธรรมการวิจัยในมนุษย์ มหาวิทยาลัยบูรพา ได้พิจารณาโครงการวิจัย

รหัสโครงการวิจัย : G-HS046/2566
โครงการวิจัยเรื่อง : Effects of Volume-Equated High Intensity Resistance Training Programs with and without Blood Flow Restriction on Morphological and Physiological Adaptations
หัวหน้าโครงการวิจัย : นายรตัญญู หลงรัก
หน่วยงานที่สังกัด : คณะวิทยาศาสตร์การกีฬา
อาจารย์ที่ปรึกษาโครงการหลัก (สารนิพนธ์/ งานนิพนธ์/ วิทยานิพนธ์/ ดุษฎีนิพนธ์) : ผู้ช่วยศาสตราจารย์ ดร.วิรัตน์ สนธิ์จันทร์
หน่วยงานที่สังกัด : คณะวิทยาศาสตร์การกีฬา
อาจารย์ที่ปรึกษาโครงการร่วม (สารนิพนธ์/ งานนิพนธ์/ วิทยานิพนธ์/ ดุษฎีนิพนธ์) : ผู้ช่วยศาสตราจารย์ ดร.กวีญา สินธารา
หน่วยงานที่สังกัด : คณะวิทยาศาสตร์การกีฬา
วิธีพิจารณา : ☐ Exemption Determination ☐ Expedited Reviews ☑ Full Board

BUU Ethics Committee for Human Research has considered the following research protocol according to the ethical principles of human research in which the researchers respect human's right and honor, do not violate right and safety, and do no harms to the research participants.

Therefore, the research protocol is approved (See attached)

1. Form of Human Research Protocol Submission Version 2: 4 September 2023
2. Research Protocol Version 1: 6 June 2023
3. Participant Information Sheet Version 2: 22 August 2023
4. Informed Consent Form Version 2: 22 August 2023
5. Research Instruments Version 2: 22 August 2023
6. Others (if any)

6.1 Training Programs Version 1 : 6 June 2023

วันที่รับรอง : วันที่ 7 เดือน กันยายน พ.ศ. 2566
วันที่หมดอายุ : วันที่ 7 เดือน กันยายน พ.ศ. 2567

สำเนา

ลงนาม *Assistant. Professor Ramorn Yampratoom*

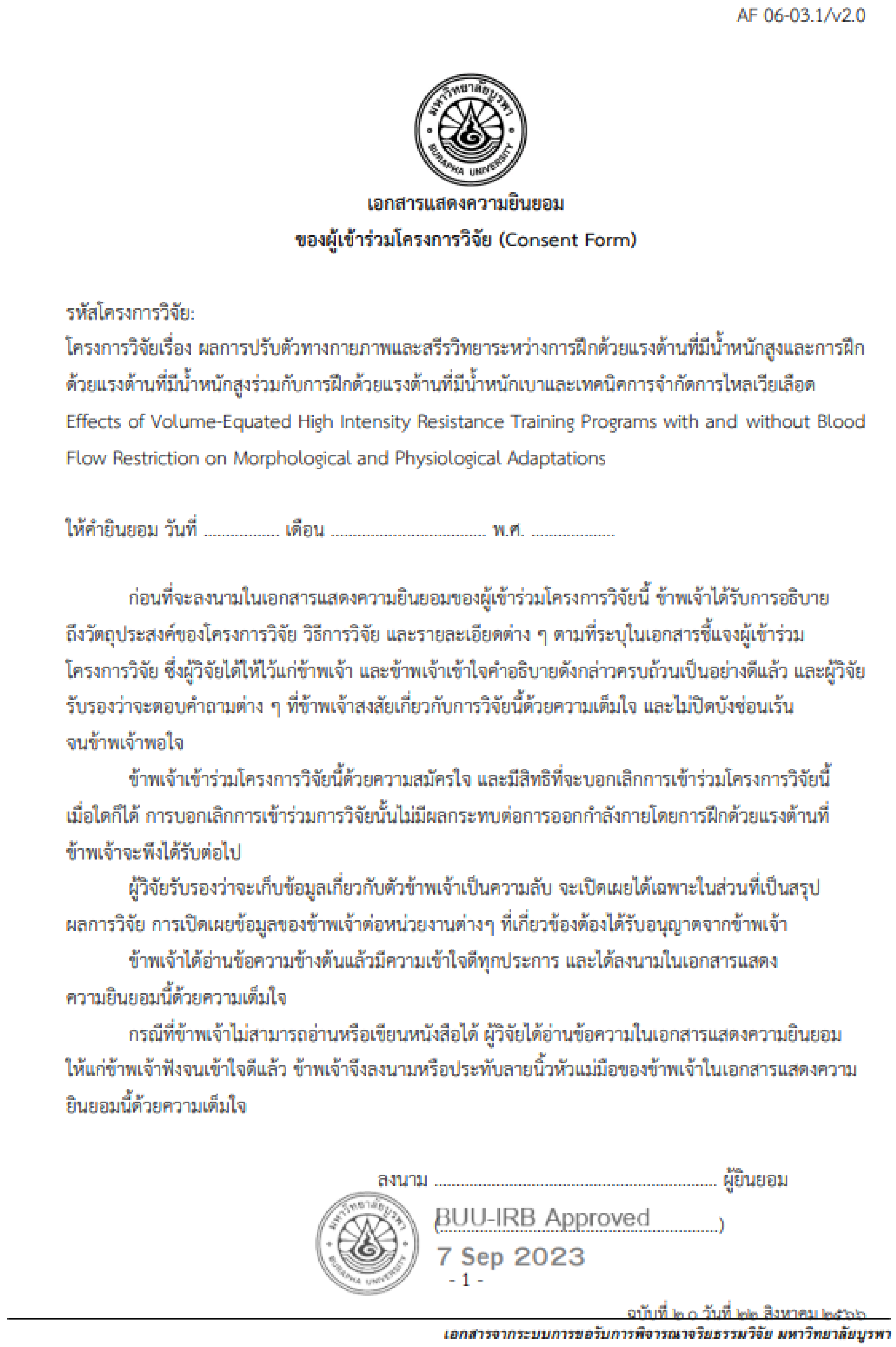
(Assistant. Professor Ramorn Yampratoom)

Chair of The Burapha University Institutional Review Board

Panel 3 (Clinic / Health Science / Science and Technology)

**** หมายเหตุ การรับรองนี้มีรายละเอียดตามที่ระบุไว้ด้านหลังเอกสารรับรอง ****

Appendix F: Consent form



AF 06-03.1/v2.0

เอกสารแสดงความยินยอม
ของผู้เข้าร่วมโครงการวิจัย (Consent Form)

รหัสโครงการวิจัย:

โครงการวิจัยเรื่อง ผลการปรับตัวทางกายภาพและสรีรวิทยาระหว่างการฝึกด้วยแรงต้านที่มีน้ำหนักสูงและการฝึกด้วยแรงต้านที่มีน้ำหนักสูงร่วมกับการฝึกด้วยแรงต้านที่มีน้ำหนักเบาและเทคนิคการจำกัดการไหลเวียนเลือด Effects of Volume-Equated High Intensity Resistance Training Programs with and without Blood Flow Restriction on Morphological and Physiological Adaptations

ให้คำยินยอม วันที่ .... เดือน .... พ.ศ. ....

ก่อนที่จะลงนามในเอกสารแสดงความยินยอมของผู้เข้าร่วมโครงการวิจัยนี้ ข้าพเจ้าได้รับการอธิบายถึงวัตถุประสงค์ของโครงการวิจัย วิธีการวิจัย และรายละเอียดต่าง ๆ ตามที่ระบุในเอกสารชี้แจงผู้เข้าร่วมโครงการวิจัย ซึ่งผู้วิจัยได้ให้ไว้แก่ข้าพเจ้า และข้าพเจ้าเข้าใจคำอธิบายดังกล่าวครบถ้วนเป็นอย่างดีแล้ว และผู้วิจัยรับรองว่าจะตอบคำถามต่าง ๆ ที่ข้าพเจ้าสงสัยเกี่ยวกับการวิจัยนี้ด้วยความเต็มใจ และไม่ปิดบังซ่อนเร้นจนข้าพเจ้าพอใจ

ข้าพเจ้าเข้าร่วมโครงการวิจัยนี้ด้วยความสมัครใจ และมีสิทธิที่จะบอกเลิกการเข้าร่วมโครงการวิจัยนี้เมื่อใดก็ได้ การบอกเลิกการเข้าร่วมการวิจัยนั้นไม่มีผลกระทบต่อการออกกำลังกายโดยการฝึกด้วยแรงต้านที่ข้าพเจ้าจะพึงได้รับต่อไป

ผู้วิจัยรับรองว่าจะเก็บข้อมูลเกี่ยวกับตัวข้าพเจ้าเป็นความลับ จะเปิดเผยได้เฉพาะในส่วนที่เป็นสรุปผลการวิจัย การเปิดเผยข้อมูลของข้าพเจ้าต่อหน่วยงานต่างๆ ที่เกี่ยวข้องต้องได้รับอนุญาตจากข้าพเจ้า

ข้าพเจ้าได้อ่านข้อความข้างต้นแล้วมีความเข้าใจดีทุกประการ และได้ลงนามในเอกสารแสดงความยินยอมนี้ด้วยความเต็มใจ

กรณีที่ข้าพเจ้าไม่สามารถอ่านหรือเขียนหนังสือได้ ผู้วิจัยได้อ่านข้อความในเอกสารแสดงความยินยอมให้แก่ข้าพเจ้าฟังจนเข้าใจดีแล้ว ข้าพเจ้าจึงลงนามหรือประทับลายนิ้วหัวแม่มือของข้าพเจ้าในเอกสารแสดงความยินยอมนี้ด้วยความเต็มใจ

ลงนาม .... ผู้ยินยอม
(...)

BUU-IRB Approved
7 Sep 2023

ลงนาม .... พยาน

(..)

<u>หมายเหตุ</u> กรณีที่ผู้เข้าร่วมโครงการวิจัยให้ความยินยอมด้วยการประทับลายนิ้วหัวแม่มือ ขอให้มีพยานลงลายมือชื่อรับรองด้วย

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