THE USAGE OF BLOOD FLOW RESTRICTION AS TRAINING INTERVENTION IN PHYSICALLY ACTIVE ADULTS AND AS REHABILITATION MODALITY IN KNEE OSTEOARTHRITIS PATIENTS

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by

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LIST OF ABBREVIATION

1-RM	-	1-Repetition Maximum
ACL	-	Anterior Cruciate Ligament
ACSM	-	The American College of Sports Medicine
ASIS	-	Anterior Superior Iliac Spine
ATP	-	Adenosine Triphosphate
BFR	-	Blood Flow Restriction
BMI	-	Body Mass Index
CE	-	Cycling Economy
CMJ	-	Countermovement Jump
COP	-	Centre of Pressure
DBP	-	Diastolic Blood Pressure
EVA	-	Ethylene-vinyl Acetate Copolymer
FDP	-	Fibrinogen Degradation Products
GH	-	Growth Hormone
GRF	-	Ground Reaction Force
HIF-1α	-	Hypoxia-inducible Factor 1α
HIIT	-	High-intensity Interval Training
HL	-	Heel Lateral
HM	-	Heel Medial
HR	-	Heart Rate
HSP	-	Heat Shock Protein
IC	-	Initial Contact
IGF-1	-	Insulin-like Growth Factor 1

IPAQ - The International Physical Activity Questionnaire

KAM - Knee Adduction Moment

LOP - limb occlusion pressure

M1-M5 - Metatarsal 1 to Metatarsal 5

MF - Midfoot

MICT - Moderate-intensity Continuous Training

mTOR - Mammalian Target of Rapamycin

MVC - Maximum Voluntary Contraction

NO - Nitric Oxide

NOS-1 - Nitric Oxide Synthase 1

OA - Osteoarthritis

PGC-1α - Peroxisome-proliferator-activated Receptor γ Coactivator 1α

PGRF - Peak Ground Reaction Force

PKF - Peak Knee Flexion

RE - Running Economy

RM-ANOVA - Repeated Measurement Analysis of Variance

RPE - Ratings of Perceived Exertion

RPM - Revolutions Per Minute

SBP - Systolic Blood Pressure

SI - Symmetry Index

SK61 - Ribosomal S6 Kinase 1

SLL - Single-leg Landing

STS - Sit-to-Stand

T1-T5 - Toe 1 to Toe 5

TAT - Thrombin-producing Marker Thrombin AT-Ⅲ Complex

VAS - Visual Analog Scale

VEGF - Vascular Endothelial Growth Factor

VO_{2max} - Maximum Oxygen Uptake

WOMAC - the Western Ontario and McMaster Universities Arthritis Index

PENGGUNAAN SEKATAN ALIRAN DARAH SEBAGAI INTERVENSI LATIHAN DALAM ORANG DEWASA YANG AKTIF SECARA FIZIKAL DAN SEBAGAI MODALITI PEMULIHAN DALAM PESAKIT OSTEOARTHRITIS LUTUT

ABSTRAK

Latihan selang intensiti tinggi (HIIT) boleh dibahagikan kepada dua fasa iaitu tempoh latihan dan selang rehat. Tidak dapat dipastikan jika wujud perbezaan dalam kesan fisiologi dan biomekanik apabila rintangan aliran darah (BFR) digunakan sebagai intervensi bagi fasa-fasa berbeza dalam HIIT. Di dalam kajian-kajian BFR yang lepas pada pesakit dengan kecederaan/masalah otot rangka, ianya lebih tertumpu pada kesan kesakitan dan fisiologi. Kesan biomekanikal latihan rintangan samada dengan atau tanpa BFR pada pesakit osteoarthritis lutut (OA) tidak diketahui. Oleh itu, kajian ini betujuan untuk menilai kesan jangka masa panjang latihan selang intensiti tinggi dengan rintangan aliran darah pada lelaki dewasa yang sihat dan kesan jangkamasa pendek BFR pada pesakit osteoarthritis lutut. Buat permulaan, seramai 32 lelaki dewasa yang sihat dibahagikan secara rawak ke dalam keadaan berikut : HIIT tanpa BFR (Kumpulan kawalan, n=11), HIIT dengan BFR semasa fasa latihan (Kumpulan kajian, n=10), HIIT dengan BFR semasa fasa selang masa (kumpulan selang rehat, n=11). Kemudian, intervensi 2 kali seminggu dilakukan selama 12 minggu. Pengambilan oksigen yang maksimum, kayuhan ekonomi, kekuatan isometrik lutut, ujian Wingate dan ujian biomekanik pendaratan sebelah kaki di lakukan pada minggu pertama, keenam dan kedua belas. Kemudiannya, seramai 15 pesakit dengan rekod OA lutut, menyempurnakan dua sesi latihan : latihan rintangan getah elastik (kumpulan kawalan) dan latihan rintangan getah elastik dengan BFR (kumpulan eksperimen). Kadar degupan jantung, kadar usaha yang dirasakan, skala analog visual, tekanan darah dan indeks biomekanik semasa ujian duduk-ke-berdiri (STS) dan berjalan di nilai sebelum dan selepas intervensi. Berdasarkan kepada keputusan kajian, dapat disimpulkan bahawa HIIT dengan BFR selama 12 minggu dapat menambahbaik kapasiti aerobik dan anaerobik bagi lelaki dewasa yang sihat. Kedua, HIIT dengan BFR tidak memberi kesan kepada pembolehubah biomekanikal semasa pendaratan sebelah kaki dalam kalangan lelaki dewasa yang sihat. Tambahan pula, penggunaan BFR sewaktu fasa selang rehat HIIT menambahbaik ekonomi kayuhan dan indeks keletihan berbanding penggunaan BFR semasa fasa latihan. Untuk pesakit OA lutut, kadar usaha yang dirasakan (RPE) lebih tinggi selepas latihan getah elastik dengan BFR. Latihan getah elastik dengan BFR meningkatkan puncak tekanan di bahagian dalam dan sisi tumit ketika berjalan. Paling utama, latihan getah elastik dengan BFR mengurangkan simetri berjalan pada peringkat awal sokongan berjalan. Akhir sekali, bagi ujian STS, bahagian OA memiliki sudut abduksi pinggul yang lebih besar berbanding bahagian yang sihat, dan daya tindakbalas dasar bagi bahagian OA adalah lebih kecil berbanding bahagian yang sihat dalam fasa bangun dari duduk dan puncak fleksi buku lali. Keputusan kajian merumuskan bahawa penggunaan BFR semasa tempoh selang rehat dapat menambahbaik kapasiti anaerobik dan ekonomi kayuhan berbanding BFR semasa fasa latihan, dan latihan getah elastik dengan BFR adalah selamat bagi pesakit OA lutut sebelah,

THE USAGE OF BLOOD FLOW RESTRICTION AS TRAINING INTERVENTION IN PHYSICALLY ACTIVE ADULTS AND AS REHABILITATION MODALITY IN KNEE OSTEOARTHRITIS PATIENTS

ABSTRACT

High-intensity interval training (HIIT) can be divided into two periods: exercise and interval period. It is unclear whether there are differences in physiological and biomechanical effects when blood flow restriction (BFR) is used for an exercise intervention in different phases of HIIT. Previous BFR studies on patients with musculoskleletal injuries/problems were focused on pain and physiological outcomes. The biomechanical effects of resistance exercise with and without BFR on patients with knee osteoarthritis (OA) are unknown. Therefore, this study evaluated the long term effect of HIIT with BFR on healthy male adults and the immediate effect of BFR resistance training on patients with knee OA. Initially, 32 healthy male adults were randomised into one of the following conditions: HIIT without BFR (Control Group, n=11), HIIT with BFR during exercise phase (Experimental Group, n=10). HIIT with BFR during interval phase (Interval Group, n=11). Then, exercise intervention twice a week for 12 weeks was performed. Maximum oxygen uptake (VO_{2max}), cycling economy, isometric knee strength, Wingate test and single leg landing biomechanical test were performed in the first, sixth and twelfth weeks. Next, 15 patients with knee OA completed two exercise sessions: elastic band resistance exercise (control group) or elastic band resistance exercise with BFR (experimental group). Heart rate, rating of perceived exertion, visual analogue scale, blood pressure and biomechanical indexes during Sit-to-Stand (STS) and gait were evaluated before and after exercise.

According to the results of study, we conclude that 12 weeks of HIIT with BFR improved aerobic and anaerobic capacity in healthy male adults. Secondly, HIIT with BFR had no effects on biomechanical variables during single leg landing among healthy male adults. In addition, the application of BFR in the interval phase of HIIT improved cycling economy and fatigue index better than when applying BFR during the exercise phase. For the OA patients, the ratings of perceived exertion (RPE) was higher after elastic band exercise with BFR. Elastic-band exercise with BFR increased the internal and lateral peak pressure of the heel during gait. Notably, the elastic band exercise with BFR reduced the gait symmetry in the early stance of gait. Finally, for STS test, the OA side had a larger hip abduction angle in the sit-off phase than the healthy side, and the ground reaction force of the OA side was smaller than the healthy side in the sit-off and peak ankle flexion phases. The present study concludes that applying BFR during the interval period of HIIT can improve anaerobic capacity and cycling economy better than BFR during the exercise phase, and elastic band exercise combined with BFR is safe in patients with unilateral OA.

CHAPTER 1

INTRODUCTION

1.1 Background of the study

Blood flow restriction (BFR) training refers to a training method that partially occludes arterial blood flow using the proximal external pressurisation provided by a unique compression device such as a pneumatic cuff or an elastic bandage (Loenneke et al., 2014; Sato, 2005). There are many methods to restrict blood flow in the lower limbs. For instance, a cuff is placed in the groin crease of the selected leg, and then the cuff is inflated to apply pressure (Figure 1.1). Blood flow restriction training has great benefits in improving cardiopulmonary function (Park *et al.*, 2010) and strength (Silva *et al.*, 2019) among athletes and promoting the rehabilitation (Li, Shaharudin & Abdul Kadir, 2021) of knee osteoarthritis (OA).

Figure 1.1 A method of applying blood flow restriction at the lower limbs

During BFR training, the leg arteries' blood flow has a non-linear relationship with the cuff pressure, whereby the leg arteries' blood flow is similar when the cuff pressure is 40%-80% of limb occlusion pressure (LOP) (Crossley et al., 2020).

Therefore, choosing a lower cuff pressure (e.g., 40% LOP may provide ischemic stimulation comparable to a higher pressure (80% LOP) but with greater comfort (Crossley et al., 2020). When formulating a BFR exercise program, other than appropriate cuff pressure, determining the suitable exercise intensity is also essential. The American College of Sports Medicine (American College of Sports Medicine, 2021) recommends high-intensity resistance exercises of more than 70% of 1 Repetition Maximum (1-RM) for muscle hypertrophy and increased strength. Interestingly, although BFR exercise's intensity is very low, its effects on increasing muscle size and strength are similar to a typical high-intensity resistance exercise (Vechin et al., 2015). However, previous studies on BFR mostly involved in continuous mode of exercise either as aerobic or resistance exercise.

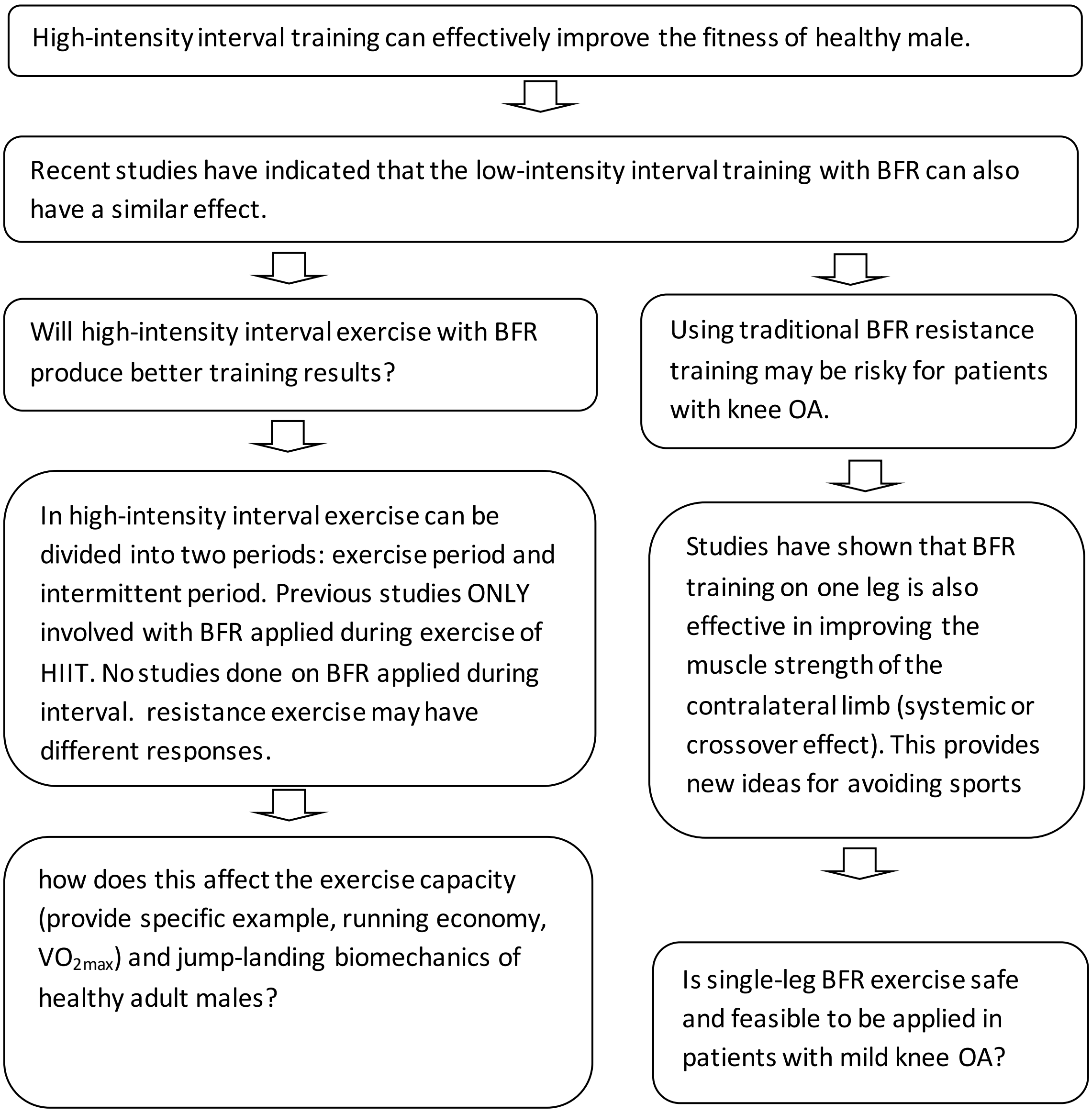
BFR intervention also improved aerobic capacity (Cook, Kilduff & Beaven, 2014; Oliveira et al., 2016; Lixandrão et al., 2018) similar to the effects of high intensity interval training (HIIT) that improved aerobic and anaerobic capacity (Eddolls et al., 2017; Gomes-Neto et al., 2017). Currently, only two studies investigated the effects of combined HIIT and BFR where they found that the BFR group showed better running economy and greater peak running velocity than the non-BFR group (Keramidas et al., 2012; Paton et al., 2017). Although these studies combined HIIT and BFR, but both studies conducted BFR during exercise phase. As we know, HIIT consists of two phases: exercise and interval phases. The phase to apply BFR will determined the outcome as Teixeira et al., (2018) observed increased blood lactate concentration during the interval phase than the exercise phase of resistance exercise with BFR.

Changes in biomechanical performance often accompany improved exercise fitness. Increasing hamstring and quadriceps muscle force through altering its strength, muscle activity, muscle length and contraction velocity are likely to reduce biomechanical risk factors related to jumping injuries (Hughes, 2014). HIIT with BFR was shown able to increase the lower limbs muscular power (Engel et al., 2019; Herbert et al., 2017; Hughes et al., 2017). However, none of the previous studies on BFR investigated its effects on biomechanical factors in healthy adults and patients population. It is not known whether there are differences in physiological and biomechanical effects when BFR is used for an exercise intervention in different phases of HIIT.

Knee OA is the main source of disability in the elderly. Unilateral knee OA leads to the reduction of gait symmetry (Mills *et al.*, 2013). Recently, low-intensity resistance training with BFR were used as a rehabilitation tool for patients with knee OA (Segal et al., 2015; Ferraz et al., 2018; Harper et al., 2019). Reducing muscle atrophy, improving muscle mass and strength, thereby increasing the knee joint's stability, is the focus of knee OA rehabilitation (Harper et al., 2019). Typical resistance exercises that increase muscle strength usually require an intensity greater than 70% 1-RM (Garber et al., 2011). However, this intensity is too high and may cause greater discomfort. Therefore, low-intensity resistance exercise with BFR may increase muscular strength at lesser pain score (Hughes et al., 2017) which indicates that it may be used as an alternative to high-intensity resistance training. Our recent meta-analysis (Li, Shaharudin & Abdul Kadir, 2021) showed that low-intensity resistance training with BFR at 60-80% LOP could effectively increase muscle strength among patients with knee pain. However, previous studies on BFR application among patients with musculoskleletal injuries/problems were focused on pain and physiological outcomes (Segal *et al.*, 2015; Harper *et al.*, 2019). Hence, the biomechanical effects of resistance exercise with and without BFR on patients with knee OA are unknown (Li *et al.*, 2021) and thus a novelty for the current work.

Despite the benefits of BFR, HIIT is divided into two phases: exercise and interval phase. It is not clear at which phase the application of BFR is better. Therefore, the first part investigated the effects of combined HIIT and BFR applied during either exercise or interval phase, among healthy adult males, while the second part investigated the immediate effects of resistance exercise with BFR among knee OA patients. Through these studies, we also examined the long-term and short term effects of BFR training, the physiological and biomechanical effects of BFR applied either in HIIT or resistance exercise, and its safety among physically active men and knee OA patients.

1.2 Theoretical framework



High-intensity interval training can effectively improve the fitness of healthy male.

Recent studies have indicated that the low-intensity interval training with BFR can also have a similar effect.

Will high-intensity interval exercise with BFR produce better training results?

In high-intensity interval exercise can be divided into two periods: exercise period and intermittent period. Previous studies ONLY involved with BFR applied during exercise of HIIT. No studies done on BFR applied during interval. resistance exercise may have different responses.

how does this affect the exercise capacity (provide specific example, running economy, VO_{2max}) and jump-landing biomechanics of healthy adult males?

Using traditional BFR resistance training may be risky for patients with knee OA.

Studies have shown that BFR training on one leg is also effective in improving the muscle strength of the contralateral limb (systemic or crossover effect). This provides new ideas for avoiding sports

Is single-leg BFR exercise safe and feasible to be applied in patients with mild knee OA?

Figure 1.2 Conceptual framework of the study

1.3 Problem statement

BFR is effective on enhancing aerobic capacity, strength and hypertrophy (Oliveira et al., 2016). HIIT also showed an excellent effect on improving aerobic capacity (Eddolls et al., 2017). Only two studies combined HIIT and BFR, and they found that the combined HIIT with BFR improved exercise performance more than HIIT only (Keramidas et al., 2012; Paton et al., 2017). However, these studies did not explore the changes in the biomechanical performance following combined HIIT with BFR intervention. Furthermore, both studies applied BFR throughout the exercise phase despite there are two phases in HIIT namely exercise and interval phases. BFR applied in exercise versus interval phase may have different physiological and biomechanical effects (Teixeira et al., 2018). Teixeira et al., (2018) observed increased blood lactate concentration during the interval phase than the exercise phase of resistance exercise with BFR. However, no studies have compared the effects of different phase of applying BFR during HIIT. By exploring the effects of applying BFR in different phases of HIIT or not applying BFR on aerobic capacity, anaerobic capacity, knee strength, cycling economy and lower limb biomechanics during single-leg landing among healthy adult males, this research can provide coaches and athletes with more diversified exercise prescriptions and provide a theoretical basis for a reasonable choice of more effective BFR application timing. In addition, by combining BFR in HIIT exercise, it may also be able to provide a more time-effective training program for people who lack exercise time. That is to produce better results in a shorter time. However, is this intervention safe to be applied in patients with knee OA still remains unanswered. This is because patients with knee osteoarthritis are more vulnerable than healthy adults, and its safety in healthy adults should be determined.

Low-intensity training with BFR increased muscle strength among patients with knee pain (Li, Shaharudin & Abdul Kadir, 2020). Bowman et al. (2019) have shown that BFR training on one leg improved the contralateral limb's muscle strength known as crossover effect. This result provides new ideas of using single-leg exercise for patients with knee OA to avoid exercising the affected leg during exercise rehabilitation. However, to the best of our knowledge, the biomechanical effects of BFR among patients, particularly those with knee OA, are not known. Gait and STS biomechanical performance are closely related to the occurrence and development of OA and the risk of falling after exercise (Christiansen & Stevens-Lapsley, 2010; Lloyd *et al.*, 2010). Blood flow restriction may cause greater muscle fatigue after exercise(de Queiros *et al.*, 2021), which may affect the biomechanical performance. Therefore, this stduy aims to investigate the immediate effects of elastic band resistance exercise with BFR on lower limb biomechanics and the feasibility of using BFR in patients with unilateral knee OA.

1.4 Research objectives

General a objective: The purpose of this study is to find evidence of the BFR safety across gender and age, which is divided into two parts.

Specific objectives: the first part involved physically active healthy adult males with the research objectives as the following:

a) To compare the effects of BFR intervention (pre-, mid-and post-intervention time points x two groups) on aerobic capacity, anaerobic capacity, knee strength, cycling economy and lower limb biomechanics during single-leg landing among healthy adult males.

b) To compare the effects of BFR intervention applied during intervals versus exercise phase (pre-, mid-and post-intervention time points x two groups) on aerobic capacity, anaerobic capacity, knee strength, cycling economy and lower limb biomechanics during single-leg landing among healthy adult males.

The second part involved knee OA patients with the research objectives as the following:

a) To compare the immediate effects (pre- and post- exercise time points x two groups)of elastic band resistance exercise with and without BFR on pain, RPE and blood pressure responses among patients with mild knee OA.

b) To compare the immediate effects (pre- and post- exercise time points x two groups) of elastic band resistance exercise with and without BFR on lower limb biomechanics during gait and STS among patients with mild knee OA.

1.5 Statistical hypothesis

Statistical hypothesis for the first part are:

a) H_O: After 12 weeks of intervention, there are no significant differences in aerobic capacity, anaerobic capacity, knee strength, cycling economy and lower limb biomechanics during single-leg landing between high-intensity interval training with and without BFR among healthy adult males.

H_A: After 12 weeks of intervention, there are significant differences in aerobic capacity, anaerobic capacity, knee strength, cycling economy and lower limb biomechanics during single-leg landing between high-intensity interval training with BFR during exercise, with BFR during the interval and without BFR among healthy adult males.

b) H_O: After 12 weeks of intervention, there are no significant differences in aerobic capacity, anaerobic capacity, knee strength, cycling economy and lower limb biomechanics during single-leg landing between high-intensity interval training with BFR during exercise versus during the interval among healthy adult males.

H_A: After 12 weeks of intervention, there are significant differences in aerobic capacity, anaerobic capacity, knee strength, cycling economy and lower limb biomechanics during single-leg landing between high-intensity interval training with BFR during exercise versus during the interval among healthy adult males.

Statistical hypothesis for the second part are:

a) H_O: There are no significant differences in the acute RPE, pain and blood pressure responses following elastic band resistance exercise with BFR among patients with mild knee OA.

HA: There are significant differences in the acute RPE, pain and blood pressure responses following elastic band resistance exercise with BFR among patients with mild knee OA.

b) H_O: There are no significant differences in the lower limb biomechanics during gait and STS following elastic band resistance exercise with BFR among patients with mild knee OA.

H_A: There are significant differences in the lower limb biomechanics during gait and STS function effects following elastic band resistance exercise with BFR among patients with mild knee OA.

1.6 Significance of the study

This study focuses on applying BFR in training and rehabilitation and is divided into two parts. The first part investigated the effects of 12 weeks BFR intervention during different HIIT phases on physiological and biomechanical variables among physically active males. These research results will enable us to understand the effects of long-term BFR interventions during different HIIT phases. The outcomes from will provide coaches and athletes with more efficient exercise prescriptions. We expect to provide more targeted exercise prescriptions which may improve physiological and biomechanical performance.

The second part investigated the immediate effects of elastic band resistance exercise with BFR on pain, functional and biomechanical variables among female patients with mild knee OA. We aimed to find a safer and more effective non-pharmaceutical intervention for patients with mild knee OA. Our findings can be applied directly by rehabilitation physicians and orthopaedic surgeons.

Therefore, the overall aspect of BFR application namely type of exercise, gender, age, and unilateral or bilateral limb exercise are investigated in the current work.

1.7 Operational definition

Table 1.1 Operational definition

Terms	Operational definition
Healthy	Have no musculoskeletal injuries and diseases in the past six months.
HIIT	HIIT is a type of interval training that alternates between short-term vigorous anaerobic exercise and less vigorous recovery periods until a participant is exhausted and unable to continue.

Mild knee OA	Diagnosed with mild knee OA using Kellgren-Lawrence severity scale, and knee pain ⩾two on a visual analogue scale (VAS) in the past week. At the same time the patient has no other medical problems such as diabetes and peripheral vascular disease.
Physically active	Participate in a training programme for a specific sport at least three times per week and total score more than 600MET-min/week based on The International Physical Activity Questionnaire (IPAQ).

CHAPTER 2

LITERATURE REVIEW

2.1 Blood flow restriction training

Blood flow restriction (BFR) training involved restricting the limbs' blood flow to increase the training effects. It was originated in Japan and also known as kaatsu. The method was developed in 1973 by Yoshiaki Sato and further improved in subsequent researches. Currently, BFR is applied in sports performance and clinical settings.

2.1.1 Mechanism of blood flow restriction

The main effects of BFR on the limb are reduced arterial blood inflow and venous blood accumulation, which will cause the limb to enter a state of relative ischemia and hypoxia (Spada, Paul & Tucker, 2022). The level of metabolic stress increases significantly because metabolites such as lactic acid cannot be effectively eliminated in this process (Teixeira, Barroso, Silva-Batista, *et al.*, 2018). Based on this, different scholars have explained the mechanism of action of BFR training from different angles. These mechanisms involve hormone secretion, regulation of protein synthesis and inhibitory synthesis regulation and muscle fibre recruitment.

2.1.1(a) Hormone secretion

Increased concentrations of anabolic hormones such as growth hormone (GH) and insulin-like growth factor 1 (IGF-1) after resistance training are beneficial to muscle growth (Kraemer & Ratamess, 2005). Takarada et al., (2000) stated that the mechanism of muscle hypertrophy after BFR training may be due to increased secretion of anabolic hormones. Due to the considerable accumulation of metabolites during exercise with restricted blood flow (Kraemer et al., 2017), the oxygen content of the internal environment is reduced. The pituitary gland is stimulated to release growth hormone (GH) through the chemosensory reflex of afferent nerves in groups III and IV (Gosselink et al., 1998). Takarada et al., (2000) found that after knee extension training with 20% of 1-Repetition Maximum (1-RM) BFR, the GH concentration increased significantly to 290 times that of resting.

Besides, the secretion of GH can stimulate the release of IGF-1 in the liver (Scott, Martin & Baxter, 1985; Geng et al., 2021). A previous study also found a significant increase in the concentration of IGF-1 after BFR exercise (Seo, So & Sung, 2016). On the contrary, Mitchell et al., (2013) showed that after BFR exercise, the GH concentration, IGF-1 and testosterone did not change, and the increase in IGF-1 concentration was not caused by GH secretion. Another study has attributed changes in IGF-1 concentration to plasma concentration (Madarame, Sasaki & Ishii, 2010). Overall, there is still inconsistent findings regarding the changes in anabolic hormones after BFR exercise, and it needs to be determined in future studies.

In addition, the menstrual cycle of young women may lead to fluctuating changes in estrogen, which in turn can affect changes in myogenic hormones such as GH and IGF-1 (Gleeson & Shalet, 2005; Southmayd & De Souza, 2017). Therefore, to minimize the impact of the menstrual cycle on the effect of the intervention, the current work decided to focus on healthy male adults. Future studies are recommended to investigate the effect of BFR application on young women at different menstrual cycle stages. Because the process of exercise producing effects is complex, estrogen may have different effects on one or more aspects.

2.1.1(b) Regulation of protein synthesis and inhibitory synthesis

Any mechanism that helps positive protein balance is beneficial to muscle growth. Mammalian Target of Rapamycin (mTOR) is considered to be the primary network that regulates skeletal muscle growth (Bodine et al., 2001) and can participate in the regulation of mRNA translation and protein synthesis (Wang & Proud, 2006). During exercise, protein kinase B is activated by IGF-1 to induce mTOR to stimulate protein translation and further promote muscle growth (Bodine et al., 2001). During BFR, the mTOR signalling pathway is stimulated by its downstream effector ribosomal S6 kinase 1 (SK61) phosphorylation, promoting protein production and inhibiting protein hydrolysis (Gundermann et al., 2014). Simultaneously, SK61 phosphorylation is conducive to the initiation and extension of protein translation (Wang & Proud, 2006). Therefore, these two approaches may be the mechanism of muscle hypertrophy caused by BFR training.

Also, heat shock protein (HSP), as a molecular chaperone in normal conditions, helps protein assembly and transport (Kiang, 1998), and plays a significant role in maintaining cell homeostasis (Simar et al., 2007). HSP can be induced in the environment of hypoxia, ischemia-reperfusion and acidosis (Kregel, 2002), such as during BFR application. Kawada and Ishii (2005) found that after two weeks of BFR training, HSP72 in rats' plantar muscles increased significantly. It indicates that in BFR training with increased ischemia, hypoxia, and increased metabolites accumulation, HSP activity may change. In contrast, Fry et al., (2010) did not find an increase in HSP70. Therefore, only some HSP, such as HSP72, may affect muscle hypertrophy. Besides, because HSP72 has the function of inhibiting the muscle atrophy signal pathway (Dodd, Hain & Judge, 2009), it can prevent the degradation of protein during the period of reduced muscle contraction activity (Naito et al., 2000).

Therefore, increased HSP may also be one of the potential mechanisms for BFR training to cause muscle hypertrophy and prevent muscle atrophy.

Increased intracellular Ca^{2+} concentration or blood flow reperfusion can activate nitric oxide synthase 1 (NOS-1) and produce nitric oxide (NO) (Schoenfeld, 2013). NO can directly activate the mTOR pathway to promote protein synthesis (Ito et al., 2013). Also, NO may activate satellite cells by synthesising the hepatocyte growth factor (HGF) during exercise and cause the proliferation of satellite cells (Anderson, 2000). Subsequently, the satellite cells continue to differentiate and merge to form new muscle fibres or merge existing muscle fibres to cause muscle fibres hypertrophy (Snijders et al., 2015). Larkin et al., (2012) observed a significant increase in NOS-1 expression after BFR training. Therefore, NO may have an essential role in the muscular adaptation produced by BFR training.

In addition to promoting protein synthesis, inhibiting the decrease of muscle growth protein expression may also have a particular effect on protein balance. Myostatin can regulate the activity and self-renewal of satellite cells (McCroskery et al., 2003). The loss of this protein will cause excessive growth of muscle tissue. It mainly inhibits the differentiation of myoblasts and myotubes through the phosphorylation of receptor-modulated Smad protein (Rebbapragada et al., 2003), thus negatively regulating muscle growth (Trendelenburg et al., 2009). A study has found that myostatin expression is reduced in BFR training (Drummond et al., 2008). Laurentino et al., (2012) divided 29 young male subjects into low-intensity BFR training group (BFR group) with 20% 1-RM, high-intensity training group with 80% 1-RM (HI group) and low-intensity training control group with 20% 1-RM (CON group). After eight weeks of knee extension training, myostatin expression in the BFR group and HI group was significantly reduced by 45% and 41%, respectively, while there was no significant change in the CON group. It indicates that the reducing expression of myostatin may lead to BFR training-induced muscle hypertrophy.

2.1.1(c) Myofibrillar recruitment

An increase in myofibrillar recruitment may also be a mechanism that causes muscle growth. According to the Henneman's size principle of myofibre recruitment, initially, the slow myofibres were recruited during exercise. As the intensity of exercise increases, muscles continuously increase recruitment of high-threshold fast myofibres (Henneman, Somjen & Carpenter, 1965). Early research has shown that the high-threshold motor unit is related to the force, muscle contraction speed, and oxygen concentration during exercise (Moritani et al., 1992). BFR can increase metabolic stress through local tissue hypoxia (Thomas, Scott & Peiffer, 2018). The low oxygen concentration further accelerates the mobilisation of high-threshold motor unit and promotes the participation of more fast muscle fibers. Therefore, the increased accumulation of metabolites during BFR training may be able to cause neuromuscular fatigue more rapidly through metabolic stimulation of group III and IV afferent nerves (Krogh-Madsen et al., 2010) or inhibition of the transverse bridge circulation (Kubota et al., 2011).

In addition, the electrical signal changes in the electromyogram can also reflect the recruitment of muscles. The study of BFR training using electromyography (EMG) showed that the frequency and amplitude of muscle discharges were significantly more in the BFR group than the control group (Loenneke. et al., 2011) during low-intensity resistance exercise, thus demonstrating the possibility of this mechanism in BFR training. However, Cook et al., (2013) did not find significantly greater muscle activation in the BFR group than in the control group. In conclusion, BFR training may also increase muscle size and strength by recruiting more motor unit, although the exact mechanism may need to be clarified by further research.

2.1.2 Application of blood flow restriction

2.1.2(a) The effect of blood flow restriction on physiological performance

In addition to the effects of BFR on strength and muscle hypertrophy (Harper et al., 2019; Loenneke et al., 2014; Shalamzari et al., 2019), BFR training may also impacted the physiological performance. A study showed that after two weeks of walking with and without BFR among healthy college students, only the BFR group's maximum oxygen consumption (VO_{2max}) increased significantly (Park et al., 2010). Abe et al., (2010) compared the effects of 8-week cycling exercise at 40% VO_{2max} intensity whereby the BFR group cycled at low-intensity for 15 minutes and the non-BFR group cycled for 45 minutes. The results showed that the VO_{2max} of the BFR group increased by 6%, while the non-BFR group showed no changes from baseline (Abe et al., 2010). Similarly, Oliveira et al. (2016) , found that low-intensity exercise with BFR is more effective in improving aerobic exercise capacity than low-intensity exercise without BFR. Furthermore, the effect of low-intensity with BFR exercise is also similar in aerobic exercise capacity to high-intensity interval training (HIIT) (Oliveira *et al.*, 2016).

The mechanism of BFR training to improve aerobic capacity is not clear. First of all, it may be due to insufficient venous blood return due to blood flow restriction, which increases the oxygen difference between arteries and veins (a-vO_2 difference). According to the Fick equation [VO_2= Heart rate (HR) x stroke volume (SV) x (a-vO_2

difference)], the increase in a-vO_2 difference leads to higher oxygen demand during exercise, thereby increasing the exercise effect (Spee et al., 2020). Secondly, the effect of tissue hypoxia on vascular endothelial growth factor (VEGF) and the increase in endothelial-dependent vasodilation during cuff release and reperfusion after BFR may also be the reasons for increased aerobic capacity (Wong et al., 2018). In summary, low-intensity aerobic exercise with BFR may be able to improve aerobic capacity by increasing a-vO_2 difference and vascular function.

2.1.2(b) Exercise rehabilitation for knee osteoarthritis

The prevalence of osteoarthritis (OA) increases gradually in the world (Cross et al., 2014). The prevalence rates of knee OA in South East Asia is comparable to Caucasian and Japanese population (Muraki et al., 2009; Nguyen et al., 2011). The prevalence of radiographic knee OA in Southeast Asia is about 35% and 31% in women and men, respectively (Fransen et al., 2011). It was estimated that the population of people age 65 years and older in Singapore, India, Malaysia, Bangladesh and the Philippines would dramatically increase more than 250% over the next three decades (Fransen et al., 2011). Therefore, it is possible that in the ageing population in these countries, knee OA will significantly impact the healthcare system (Nguyen, 2014). The Global Burden of Disease Study show that knee osteoarthritis is one of the fastest-growing orthopaedic surgical diseases and ranks second among the causes of disability worldwide (Cross et al., 2014). The risk of disability resulting from knee OA is equal to cardiac disorder and more than any other medical condition in the older population (Kramer, Yelin & Epstein, 1983; Guccione, 1994). The clinical symptoms of knee OA include pain, stiffness, joint swelling and impaired motor function (Moskowitz, 2007), which will lead to inconvenience in daily life.

Restoring skeletal muscle function by improving muscle mass and strength, is a priority for rehabilitation. However, high-intensity strength training among rehabilitating populations with musculoskeletal injuries are challenging due to limb function deterioration, pain and risk of injury (Hoyt et al., 2015). Therefore, BFR training provides them with a novel way to restore muscle function. In a study (Ferraz et al., 2018), 34 arthritic patients were divided into three groups: 12 weeks of either high-intensity resistance training (80% 1-RM), low-intensity resistance training (30% 1-RM) with or without BFR. Limb occlusion pressure (LOP) at 70% was used in BFR training to limit blood flow to patients with knee OA (Ferraz et al., 2018). The results showed that patients in the BFR and the high-intensity resistance training grous had improved muscle strength and knee OA function. Interestingly, BFR training can also reduce joint pressure which further reduce pain, thus it may become a potential auxiliary rehabilitation method for OA treatment (Ferraz *et al.*, 2018; Li, Shaharudin & Abdul Kadir, 2021). However, none of the previous studies investigated the effects of BFR on lower limb biomechanics during gait among knee OA patients.

It is impossible to put BFR on the injured leg with knee OA and pain (Harper et al., 2019). Therefore, it is very difficult to directly improve the injured limb's muscle strength through BFR training. Fortunately, a study (Bowman et al., 2019) have shown that BFR training on one leg effectively improves the contralateral limb’s muscle strength (i.e., systemic or crossover effect). It is speculated that this may be due to a greater metabolic stress caused by blood flow restriction that results in an increase in systemic circulating myogenesis-related hormones, which in turn benefits the contralateral limb (Bowman et al., 2019). This finding provides a new idea for knee

OA patients to use single-leg exercise instead of double-leg exercise to avoid exercising the affected leg during exercise rehabilitation. However, for patients with bilateral osteoarthritis, this program of exercise may not be suitable. Therefore, it is speculated that this problem may be solved by developing hip exercise program in the future.

We have published a systematic review with meta-analysis of the effects of BFR training on patients with knee injuries on the American Journal of Physical Medicine & Rehabilitation (Li, Shaharudin & Abdul Kadir, 2021, Appendix A). We conclude that muscle strength was greater after low intensity resistance training with BFR compared with low intensity resistance training without BFR intervention, whereas pain score was lower in the low intensity resistance training with BFR than the high intensity resistance training intervention. Hence, low intensity resistance training with BFR is a potential rehabilitation modality for patients with knee injuries. Another paper was also published on Scientific Reports in 2021 regarding the effects of resistance training on gait velocity among knee OA patients.

2.1.3 Methodological issues of blood flow restriction training

2.1.3(a) Types of blood flow restricted devices

BFR training uses the dedicated inflatable cuff to apply external pressure on upper or lower limbs (Liu *et al.*, 2021). The BFR devices used in the related study can be divided into inflatable and non-inflatable. Among them, the inflatable type includes medical sphygmomanometers (Araujo et al., 2017), unique elastic inflatable cuffs (Yasuda et al., 2012) and nylon inflatable non-elastic cuffs (Freitas et al., 2017). Non-inflatable types include elastic bandage with buckle (Yamanaka, Farley & Caputo, 2012), elastic bandage without buckle (Luebbers et al., 2014) and an inelastic tourniquet (Shinohara et al., 1997)).

Different BFR devices have varied materials, widths, ease of application, cost and pressure. Fitness groups and athletes preferred a simple and low cost BFR device. In contrast, research areas have higher requirements particularly to quantify the pressure accurately. Studies on the cuff's material found that in the same width and pressure, the elastic cuff and the nylon cuff have the same pressure in the resting state (Jeremy et al., 2013) and exercise state (Loenneke et al., 2014). The same acute response can be observed during BFR training using either elastic or nylon inflatable cuffs of the same width and pressure (Dankel et al., 2017).

In the literature, the upper limb cuffs width ranges from 3 to 5 cm (Yasuda et al., 2015; Jessee et al., 2018), and 5 to 18 cm for lower limb cuffs (Loenneke et al., 2017; Sousa et al., 2017), whereby different widths have different levels of BFR. The wide blood cuffs applied the same pressure of BFR (Crenshaw et al., 1988), rate of perceived exertion (RPE), pain score (Rossow et al., 2012), and arterial occlusion rate under the same pressure (Loenneke et al., 2013). Despite the above differences in blood flow-restricted cuffs of different widths, some studies did not account for cuff width (Kacin & Strazar, 2011; Maass et al., 2016; Lixandrão et al., 2018), which reduced comparability between studies. Location of the cuff may determine the strength outcomes. Blood flow restriction usually acts on the muscle groups around the cuff (Bowman *et al.*, 2019). For example, wearing a cuff on the upper thigh is mainly beneficial to the muscles near the knee and hip. So training that need to focus on specific muscle groups can be applied through BFRT.

2.1.3(b) The amount of pressure

The cuff pressure is an essential factor in BFR training. Related studies on BFR training use a single absolute pressure range for the upper and lower limbs corresponding to 50-270 mmHg (Yasuda et al., 2015; Sugiarto et al., 2017) and 160-260 mmHg (Madarame et al., 2008). However, the same pressure does not necessarily limit everyone's blood flow to the same level. The pressure of BFR will vary due to differences in cuff width (Crenshaw et al., 1988) and individual characteristics such as limb circumference (Jeremy et al., 2012). Therefore, using absolute pressure for BFR training may not be appropriate. Presently, seeking quantitative indicators for cuff pressure and exploring safe and effective pressure range is the focus of many studies on BFR training.

There are a number of ways to quantify cuff pressure. Studies using inflatable BFR cuffs primarily use resting systolic blood pressure (SBP) (Kim et al., 2017) and resting limb occlusion pressure (LOP) (Counts et al., 2016) to quantify the BFR pressure. A study using elastic bandages use perceived pressure to quantify the pressure of BFR because external pressure can not be quantified (Wilson et al., 2013). There is also a study using arterial blood flow measurements to quantify the BFR pressure (Laurentino et al., 2008). Practitioners rarely use quantifiable BFR devices due to time and financial costs hence they typically rely on patient's feedback. For instance, a level 7 out of 10 subjective pressure without discomfort and pain can be used as a standard for BFR training (Wilson et al., 2013). A follow-up study showed that this method improved muscle mass and strength (Salyers et al., 2018). Therefore, when applying blood flow restriction, the cuff pressure should be set accordingly.

It should be noted that the initial pressure (i.e., the cuff pressure on the limb) will have a certain effect on BFR (Karabulut et al., 2011). For a quantifiable BFR device pressure, the initial pressure is preferably set around 40 to 60 mmHg (Karabulut et al., 2011). For elastic bandages that cannot be quantified, given the different individuals' perceptions of actual pressure, Karabulut et al., (2011) suggested that participants can adjust the bandage's tightness based on ability to complete an exercise on the same limb (i.e., knee flexion extension if the cuff is placed on the thigh) for 30 times comfortably. If the participant can not repeat the exercise 30 times, the bandage can be further loosened.

The commonly used cuff pressures are 40% to 80% LOP (Mouser *et al.*, 2017; Ilett *et al.*, 2019; Singer *et al.*, 2020; Morley *et al.*, 2021). At low training intensity with 20%-30% 1-RM (Giles *et al.*, 2017; Harper *et al.*, 2019), the increase in pressure of the cuff from 40% to 80% LOP will cause an increase in muscle size and isometric torque (Dankel et al., 2017). However, at 40% 1-RM training intensity, this training effect is not better than 20% 1-RM (Lixandrão et al., 2015). A recent study has also pointed out that the leg arteries' blood flow has a non-linear relationship with the cuff pressure. When the cuff pressure is 40%-80%, the leg arteries' blood flow is similar (Crossley et al., 2020). Overall, if the training intensity of BFR training is around 30% 1-RM (Giles *et al.*, 2017), cuff pressure above 40% LOP may have a similar effect on muscle growth. Considering the discomfort caused by greater pressure, the recommended cuff pressure is 40% LOP (Crossley *et al.*, 2020). Besides, the amount of subcutaneous fat (Shaw & Murray, 1982), gender and ethnicity (Jessee et al., 2016) may also affect LOP, and these factors need to be considered when using BFR cuffs.

2.1.3(c) Load weight

Load weight refers to the weight that athletes resist during exercise. It is an essential factor when setting up an exercise program. The strength indicators commonly used in the current BFR training related to a study are the percentage of 1-RM (Ratamess, 2009), maximum voluntary contraction (MVC), and RPE. 1-RM is the most commonly used intensity indicator for resistance exercise with equipment. MVC is an indicator for grip strength (Kim et al., 2017) and single-joint exercises (Kacin & Strazar, 2011), while RPE is a good indicator for own body weight (Kang et al., 2015) and water resistance exercises (Araújo et al., 2015). Research on BFR training involved load weights ranging from 5% MVC (Natsume et al., 2015) to 80% 1-RM (Laurentino et al., 2008) and RPE grades 9-13 (Araújo et al., 2015). A meta-analysis found that low-intensity resistance training with BFR with an intensity of 15%-30% 1-RM or MVC seems to have a better effect on muscle hypertrophy in healthy adults than without BFR (Loenneke et al., 2012).

For BFR, higher exercise intensity may not necessarily provide better changes. The comparison of the two studies shows that 50% 1-RM intensity (Takarada, Sato & Ishii, 2002) and 30% 1-RM intensity (Madarame et al., 2008) of lower limb resistance training have similar effects on muscle hypertrophy. Besides, in the acute study of BFR training, it was found that 40% MVC compared with 20% MVC BFR knee extension exercise can cause more significant fatigue, and the subjects tend to choose 20% MVC (Cook et al., 2007). A study has suggested that more than 40% to 50% of MVC training intensity may cause pressure to be greater than systolic blood pressure and cause arterial blood flow occlusion (Yamada et al., 2004). In another study, it was found that when BFR training is performed with 50% to 60% MVC, the quadriceps arterial blood flow occludes with each exertion (Sadamoto, Bonde-Petersen & Suzuki, 1983). Resistance training with arterial blood flow occlusion not only causes tremendous pain, but it can also cause safety issues such as temporary numbness or subcutaneous