Feasibility of Blood Flow Restriction Resistance Exercise for Patients with Intermittent Claudication

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for the degree of Doctor of Philosophy

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Candidate Declaration

I hereby declare that:

1. I have not been enrolled for another award of the University, or other academic or professional organisation, whilst undertaking my research degree.

2. None of the material contained in the thesis has been used in any other submission for an academic award.

3. I am aware of and understand the University's policy on plagiarism and certify that this thesis is my own work. The use of all published or other sources of material consulted have been properly and fully acknowledged.

4. The work undertaken towards the thesis has been conducted in accordance with the SHU Principles of Integrity in Research and the SHU Research Ethics Policy.

5. The word count of the thesis is **51441** (from chapters 1 to 7)

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Abstract

Intermittent Claudication (IC) is a common and debilitating symptom of peripheral arterial disease (PAD) resulting in significant reduction in exercise performance and quality of life. Supervised exercise programmes are part of first-line treatment for IC proving highly effective for improving exercise performance and alleviating symptoms. Despite this, supervised exercise programmes have poor adherence in part to patients' inability to tolerate IC related pain during walking exercise highlighting the need for alternative exercise modes. Blood flow restriction resistance exercise (BFR-RE) is a technique that facilitates local muscle hypoxia during resistance exercise to induce hypertrophy, strength, and muscular endurance. BFR-RE presents an exciting alternative modality to improve exercise performance in IC patients though requires research on safety, feasibility, and efficacy. This research explored the acute perceptual, affective, and physiological responses to resistance exercises performed at low-load with BFR (LL-BFR), low-load (LL) and moderate-load (ML) in healthy young and older adults; examined the inter-day reliability of a physical function test battery in IC patients sought to determine suitability of the test battery and smallest worthwhile change for each measure; and conducted a randomised controlled trial to evaluate the safety, feasibility, and efficacy of an 8-week LL-BFR resistance exercise programme in IC patients. No adverse events were recorded during this body of work that was attributed to the protocols or procedures administered. LL-BFR was shown to be more demanding than LL and ML predominately through increased pain ($p \leq 0.024$, $d = 0.8 – 1.4$). However, this did not lead to decrements in affective response and fatigue post exercise. Excellent reliability (≥ 0.92 ICC) of the physical function test battery was observed in IC patients and the minimum likely change (76% chance) was calculated for each measure. The feasibility trial observed high adherence (LL-BFR = 78.3%, LL = 83.8%) and completion rates (LL-BFR = 93%, LL = 87%). Significant clinical improvement (>35 m) in the six-minute walk test (6MWT) was achieved in 86% of patients in LL-BFR but only 46% of patients in LL. Additionally, time to claudication pain during 6MWT was likely increased (44.7 s [20.8, 68.6]) for LL-BFR and likely unchanged (4.4 s [-32.4, 23.6]) for LL. This thesis supports BFR-RE as a safe, feasible and potentially effective exercise mode for IC patients.

Statement of Originality

I hereby declare that all the work contained in this thesis is original and was undertaken by the author unless otherwise stated below. Where reference is made to the work of others, citations are included with the authors' name and year of publication.

The PhD programme was supported under Sheffield Hallam University Graduate Teaching Assistance Scholarship Scheme, following successful application which involved presenting the initial research protocol that was designed by Mr Tom Parkington (TP). Prof Markos Klonizakis (MK), Prof David Broom (DB) and Dr Tom Maden-Wilkinson (TWM) supervised the PhD programme and accordingly reviewed and developed the initial research protocol.

The first Experimental Chapter represents work conducted by TP, MK, DB and TWM. TP was responsible for the study design, ethics application, recruitment, data collection, data analysis, manuscript preparation and submission where it is currently under review. MK, DB and TWM provided supervisory and editorial support throughout from study design to submission.

The second and third Experimental Chapter represents work conducted by TP, MK, DB, TWM, Mr Shah Nawaz (SN) and Mr Noman Shahzad (NS). TP was responsible for the study design, local ethics application, NHS ethics application, patient recruitment, data collection, data analysis, manuscript preparation and submission. MK, DB and TWM provided supervisory and

editorial support throughout from study design to submission. SN was the clinical lead of the project overseeing study design, NHS ethics application and patient recruitment. NS assisted with patient recruitment.

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Publications and Conference presentations

Peer reviewed full-length articles

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Preparing for Submission: Parkington, T., Broom, D., Maden-Wilkinson, T., Shahzad, N., Nawaz S. and Klonizakis, M. (2022). Low-Load Resistance Exercise with Blood Flow Restriction for Patients with Intermittent Claudication: A Randomised Controlled Feasibility Study. *Vascular Medicine.*

Conference Presentation

British Society of Gerontology Annual Conference. August 2021. *Poster Presentation:* Comparative Affective Responses Between Blood Flow Restriction and Conventional resistance Exercise in Older Adults.

Submitted: European Society for Vascular Surgery Annual Meeting. September 2023. *Poster Presentation:* A novel training approach to improve

walking performance, uptake and compliance in patients suffering with intermittent claudication.

Overview of Thesis

This thesis scopes and explores the safety, feasibility and preliminary efficacy of blood flow restriction resistance exercise (BFR-RE) in patients with Intermittent Claudication (IC). The thesis begins with an introduction that provides the context to the thesis, justifies the value of research, and identifies the research objectives and questions (Chapter One). Chapter Two reviews the literature and identifies the factors and mechanisms contributing to reduced exercise performance and functional decline in patients with IC and outlines the current clinical treatment practices. Additionally, the current understanding of the mechanisms surrounding BFR-RE, and recommended exercise protocols are explored. From the reviewed literature, a rationale for BFR-RE in patients with IC is presented. The research methodology is presented in Chapter Three. The Chapter provides the overview of the Experimental Chapters, and the inclusion of key variables and techniques are justified. Chapter Four, Five and Six make up the three Experimental Chapters that will address the specific research objectives and questions. Chapter Seven will interpret and explain the meaning, importance and significance of the findings form the Experimental Chapters and make recommendations for future research. Additionally, the reflections of the researcher through the PhD programme are presented.

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1 Introduction

The role of a Clinical Exercise Physiologist is to manage long-term, non-communicable health conditions using scientific rehabilitative exercise prescription. The Clinical Exercise Physiologist objective will be to optimise physical function and health and promote long-term wellbeing through lifestyle modification and behaviour change.

Peripheral arterial disease (PAD) is a type of cardiovascular disease that describes hardened, narrowed, or obstructed arteries that supply to the lower extremities by the build-up of fatty plaques. PAD affects approximately 13% of adults >50 years old worldwide and ≈ 500,000 people in the United Kingdom are diagnosed (Bhatnagar et al., 2015; Crawford et al., 2016). There is limited evidence of the prevalence of PAD. However, it appears PAD rates between men and women are comparable (Fowkes et al., 2017), PAD rates in general population appear higher for black people (6.7%) compared to white (3.5%) and Asian (3.7%) people (Vitalis et al., 2017) and global estimates of PAD report higher incidences of PAD in lower to middle income countries compared to high income countries (Fowkes et al., 2017) though differences in PAD rates between different regions in the UK are negligible (Bhatnagar et al., 2015).

Intermittent Claudication (IC) is a common and debilitating symptom of PAD which is cramp-like pain in the legs and/or buttocks that is consistently induced by walking and relieved by rest (Gerhard-Herman et al., 2017). IC occurs due to an impaired ability to increase blood flow and oxygen delivery to sufficiently match the metabolic demands of lower extremity muscles during exercise (Morley &

Sharma, 2018). Patients will frequently choose to avoid physical activity as a defence to manage IC and report feelings of anxiety and embarrassment (Gorely et al., 2015). Over time, PAD and a reduced overall physical activity contributes to a substantial loss in exercise performance and quality of life (QoL), developing into significant morbidity and mortality (Morley & Sharma, 2018). In addition to these clinical concerns, IC treatment generates substantial costs for the health care system (Hirsch et al., 2008; Mahoney et al., 2010).

Supervised exercise programmes are recommended as part of first-line treatment for IC, aimed to improve patients exercise performance, leg symptoms and QoL, and slow the progression of PAD (Gerhard-Herman et al., 2017). Clinical guidelines recommend exercise programmes include intermittent walking to near maximal or maximal pain, three times a week (Hirsch et al., 2006). The effectiveness of supervised exercise programmes as part of treatment for IC is unquestionable (Lane et al., 2017). For instance, patients with IC who complete 12-week supervised exercise show significant clinical improvement in walking performance (Gommans et al., 2014) and reduced overall cardiovascular mortality by 52% and morbidity by 30% within a maximum of 13 years of follow-up (Sakamoto et al., 2009). Despite this, exercise programmes have poor uptake and compliance in part to patients' inability to tolerate pain during walking exercise (Gorely et al., 2015). There are few alternative treatment options available for IC. Given the effectiveness of supervised exercise programmes, the poor uptake and compliance to these programmes is a great concern. Therefore, as walking exercise is painful for patients with IC and exercise performance reduces with time if no treatment is followed (Klonizakis et al., 2018), alternative

and preferably claudication pain free exercise modes must be available. This requires further research on novel exercise modes both on safety, feasibility and effectiveness.

Blood flow restriction (BFR) is a technique which utilises an external compression around the upper part of the limb to disrupt the normal blood flow around the area of external compression. BFR in combination with low-load resistance exercise (BFR-RE) has consistently shown to induce hypertrophy, strength and muscular endurance in young and older adults (Centner et al., 2019; Fahs et al., 2015; Kacin & Strazar, 2011). In addition, the BFR-RE stimulus may produce beneficial vascular adaptations that enhances blood flow and gas/metabolite exchange contributing to an increased exercise capacity (Ferguson et al., 2018; Hunt et al., 2013). The utility of BFR-RE to mitigate the impact of sarcopenia on physical function in older adults at risk of mobility loss is encouraging (Cook et al., 2017; Cook & Cleary, 2019; Hughes et al., 2017). Furthermore, BFR-RE offers a more time efficient and effective approach to matched resistance exercise without BFR and a less painful approach to high-load resistance exercise (HL-RE) for patients in musculoskeletal rehabilitation (Hughes et al., 2017).

Much of the practical implications concerning BFR-RE in a clinical setting has been directed towards using the technique to induce hypertrophy and strength for populations where traditional HL-RE is challenging, unattainable or contraindicated. While this is undoubtably important, sometimes overlooked in the BFR literature is the chronic exposure to hypoxia from the BFR stimulus that can enhance oxidative capacity, enabling improved exercise performance

(Ferguson et al., 2018; Lundby et al., 2009). Such adaptations from BFR-RE could be valuable to patients with chronic limb ischemia. Though the absence of research regarding BFR-RE and PAD limits the possibility of its clinical utility until its safety and feasibility, and following that, its clinical and cost effectiveness is proven.

The Medical Research Council (MRC) provide guidance for developing and evaluating complex interventions. The MRC recommends a carefully phased and systematic approach to interventions that begins by identifying relevant evidence and theory, then conducting feasibility or pilot trials where procedures and protocols can be tested (Skivington et al., 2021). Modelling an intervention before a full-scale evaluation can identify weaknesses, lead to refinement, and indicate whether a full-scale trial is warranted (Skivington et al., 2021). The purpose of the feasibility trial is to provide estimates of recruitment and retention and acceptability of procedures and protocols. Therefore, the evaluation of feasibility studies provides a valuable insight into whether an intervention is plausible or effective and how it can be optimised.

This research will be the first to apply BFR-RE to patients with IC. In accordance with MRC guidance, the first objective will be to compare the acute perceptual, affective and physiological responses to lower-body resistance exercise between low load with BFR (LL-BFR) and low load (LL) and moderate load (ML) without BFR in healthy young and older adults, to evaluate the extent BFR is tolerated (Chapter Four). The second objective will be to quantify the reliability of a physical function test battery for patients with IC and determine the smallest worthwhile

change in test scores to assess the effects of exercise programmes at an individual level (Chapter Five). The third objective will be to explore the safety and feasibility of a randomised control trial to assess the efficacy of a BFR-RE programme for patients with IC (Chapter 6). The specific thesis research questions are:

First Experimental Chapter

Does the addition of BFR increase the acute perceptual, affective and physiological response during lower-body resistance exercise?

Does the type of lower-body resistance exercise (multi-joint or single-joint) when performed with BFR effect the acute perceptual, affective and physiological response?

Second Experimental Chapter

What is the inter-day reliability of a physical function test battery in patients with IC?

What is the minimum magnitude of change in test scores from the physical function test battery that is required to be considered a likely change (76% chance) in patients with IC?

Third Experimental Chapter

Is an 8-week BFR-RE programme safe and feasible for patients with IC?

Does an 8-week BFR-RE programme improve exercise performance in patients with IC?

This research will contribute to the body of knowledge regarding the clinical utility of BFR-RE by addressing the question is BFR-RE safe and feasible for patients with IC? This research has the potential to become the foundation for future research that examines the extent BFR-RE is useful to patients with IC with the objective to support clinical exercise physiologists with their challenge of prescribing effective exercise programmes.

2 Literature Review

The following chapter is a narrative literature review of the critical aspects of the current knowledge of PAD aetiology and treatment, and the acute and chronic responses of BFR-RE. This permitted a broader scope of the key literature that supported a theoretical rational for the implementation and potential benefits of BFR-RE in IC patients. Key systematic reviews and meta-analysis relating to the exercise training in PAD (Lane et al., 2017), and the acute and chronic responses of BFR-RE (Hughes et al., 2017; Lixandrao et al., 2018; Neto et al., 2017; Pearson & Hussain, 2015; Slysz et al., 2016) were considered in this review and informed the development of the protocols used in this research.

2.1.1 Peripheral Arterial Disease

In this thesis, PAD refers to atherosclerosis in the lower extremities. Other terms often used for this condition clinically include peripheral vascular disease, peripheral arterial occlusive disease, and lower extremity arterial disease.

PAD is a condition that describes a blood circulation disorder of the arteries that supply the lower extremities. PAD is caused primarily by systemic atherosclerosis, which affects the structure and function of aorta and arteries of the lower extremities (Gerhard-Herman et al., 2017). Therefore, understanding the pathology of PAD is best considered through the study of atherosclerosis in general.

Atherosclerosis is a chronic inflammatory condition that is complex though it has been efficiently described through consideration of three stages; lesion initiation,

lesion progression, and plaque complications (Libby, 2000), as is depicted in **FIGURE 1**. The initiation of atherosclerosis occurs following endothelial cell injury. This can be caused via several different mechanisms including oxidative stress through abnormal regulation of reactive oxygen species, hypoxia, turbulent blood flow and shear stress; environmental irritants such as tobacco; hyperlipidaemia and bacterial or viral infection (Libby, 2000). At the endothelial cell injury site, the intima is exposed allowing substances such as fats, cholesterol, platelets, cellular waste products and calcium to collect. With the accumulation of these materials, oxidation of lipoproteins initiates inflammation. As a response, mononuclear leukocytes are recruited to the cell injury site. Once mononuclear leukocytes collect in the intima, they typically accumulate lipid and become foam cells. These foam cells comprise the earliest recognisable stage of atherogenesis, a yellow linear elevation of the intima referred as the ‘’fatty streak’’. Atherosclerosis at this stage is reversable. However, increasing accumulation of foam cells in the intima stimulates an abnormal proliferation of smooth muscle cells causing the plaque to become increasingly fibrous transforming the fatty streak into a more advanced plaque. As the atherosclerotic plaque develops and enlarges it progressively narrows lumen and obstructs blood flow.

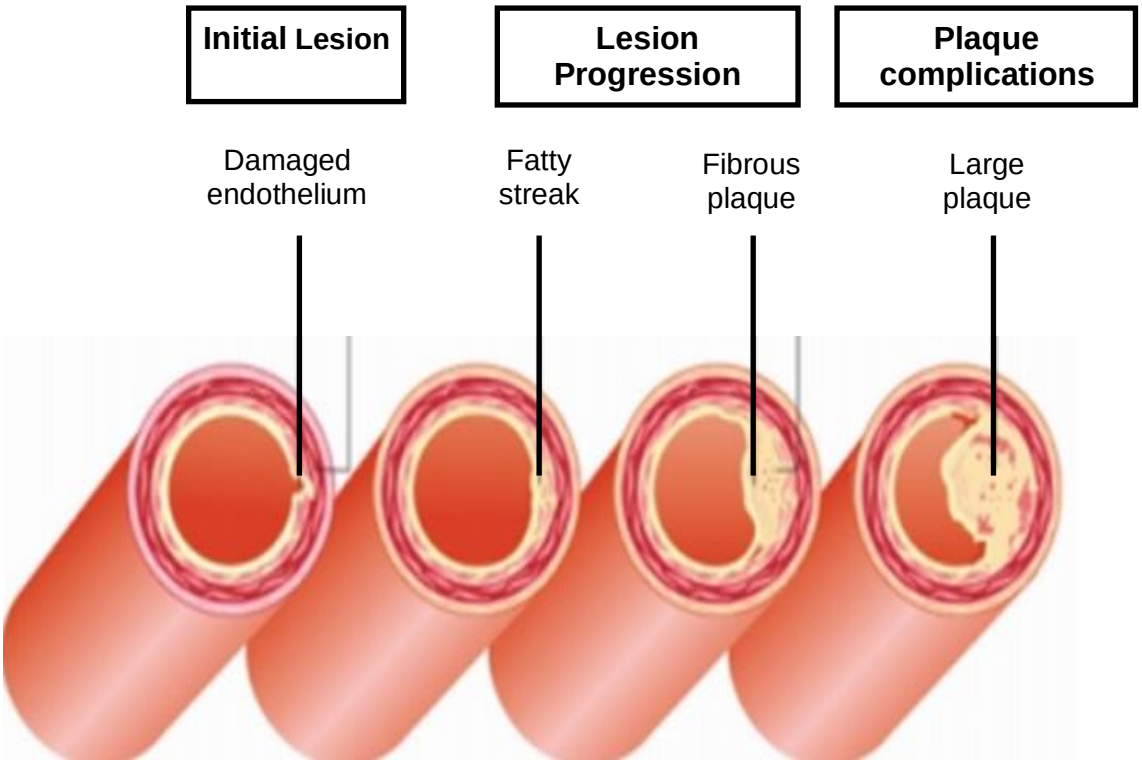


FIGURE 1: Progression of atherosclerosis in cardiovascular disease (Libby, 2000).

2.1.2 Prevalence and Risk Factors of PAD

The global burden of PAD is large and rising. Recent estimates of prevalence of PAD worldwide exceed 200 million people, a 34% increase since estimates in 2005 (Fowkes et al., 2017). Uncommon among younger people, the prevalence of PAD rises sharply with age and affects a substantial proportion of older people, similarly between men and women (**FIGURE 2**). Approximately 50% of people with PAD are asymptomatic (Song et al., 2019). The prevalence of the classic symptomatic presentation of PAD, IC, increases with age affecting <0.1% of people aged <50 years and 6 – 31% of people aged 65 – 74 years (Norgren et al., 2007). In the UK, ≈ 500,000 people are diagnosed with PAD with northern regions reporting the highest prevalence (Bhatnagar et al., 2015).

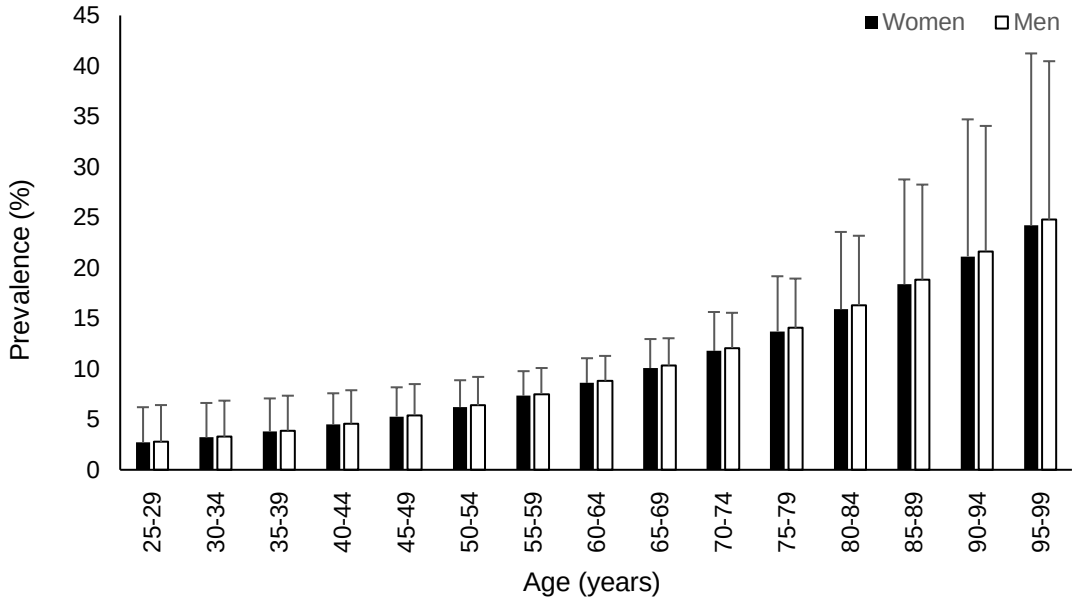


FIGURE 2: Estimated age-specific prevalence of women and men living with PAD in high-income countries (Fowkes et al., 2013). Data are % [95% CI].

Risk factors for PAD have been determined between cross-sectional associations between current disease status and current risk factor measurements and are typical risk factors of atherosclerotic disease. Cigarette smoking, hypertension, hyperlipidaemia, diabetes mellitus, family history of vascular diseases and age have all demonstrated strong, graded, and independent associations with risk of clinically significant PAD (Joosten et al., 2012; Sigvant et al., 2016). Obesity, and ethnicity are other notable risk factors but have moderate associations to disease status (Criqui & Aboyans, 2015; Tendera et al., 2011). Several biomarkers are novel risk factors, including C-reactive protein, fibrinogen, and plasma homocysteine (Ridker et al., 2001).

2.1.3 Clinical Presentation and Prognosis of PAD

Flow-limiting atherosclerotic plaques are major contributors towards the development of ischaemic symptoms in PAD. However, it is important to understand that despite similar extent and level of disease progression, presentation of PAD can vary considerably between patients. The Fontaine Stages or Rutherford categories both categorise the different presentations of PAD (**TABLE 1**).

TABLE 1: Classifications of PAD: Fontaine stages and Rutherford categories (Aboyans et al., 2018).

Fontaine			Rutherford		
Stage		**Symptoms**	**Grade**	**Category**	**Symptoms**
I		Asymptomatic	0	0	Asymptomatic
II	IIa	Non-disabling intermittent claudication	I	1	Mild claudication
			I	2	Moderate claudication
	IIb	Disabling intermittent claudication	I	3	Severe claudication
III		Ischemic pain at rest	II	4	Ischemic pain at rest
IV		Ulceration or gangrene	III	5	Minor tissue loss
			III	6	Major tissue loss

Among patients with PAD who are asymptomatic, 7% [95% CI: 4, 11%] are likely to develop symptoms over 5 years (Sigvant et al., 2016). However, a subset of this group may have severe disease without symptoms, which is related to their inability to exercise enough to present classic symptoms, qualified as ‘masked PAD’. Patients who are older and have multiple comorbidities are more at risk of masked PAD and consequently often follow a specific path from asymptomatic PAD shifting rapidly to severe PAD (Aboyans et al., 2018).

The most common presentation of PAD is IC, which describes fatigue, discomfort, cramping, or pain of vascular origin in the muscles of the lower extremities that is consistently induced by exercise and relieved by rest (Gerhard-Herman et al.,

2017). This is likely due to adequate arterial perfusion to the lower extremities at rest, though during exercise the increased metabolic demand of the exercising limbs is not adequately met, leading to symptoms of ischaemic pain. Among patients with IC, most (approximately 75%) improve spontaneously or remain stable. Though with increasing impairment of underlying blood flow, 21% [95% CI; 12, 29%] of IC patients symptoms worsen over 5 years, developing into more severe claudication or critical limb ischemia which describes resting pain and tissue loss including ulceration or gangrene (Sigvant et al., 2016).

Few deaths are directly attributed to PAD, though its presence has potent morbidity and mortality implications. Many patients with PAD also have concomitant coronary artery and cerebrovascular disease (Aboyans et al., 2018). Incidence rate for cardiovascular mortality over 5 years in asymptomatic PAD is 9% [95% CI; 7, 12%] and symptomatic PAD 13% [95% CI; 9, 17%] (Sigvant et al., 2016).

2.1.4 Diagnosis of PAD and IC

Diagnostic approach for PAD is depicted in **FIGURE 3** and begins with clinical history and a physical examination. The aim is to begin to distinguish PAD from other causes of leg pain such as neurological disorders, inflammatory muscle diseases or osteoarthritis and identify risk factors for atherosclerotic disease in consultation and clinically history. Following clinical examination, the ankle-brachial pressure index (ABPI) is the first step to confirm the clinical diagnosis (**TABLE 2**).

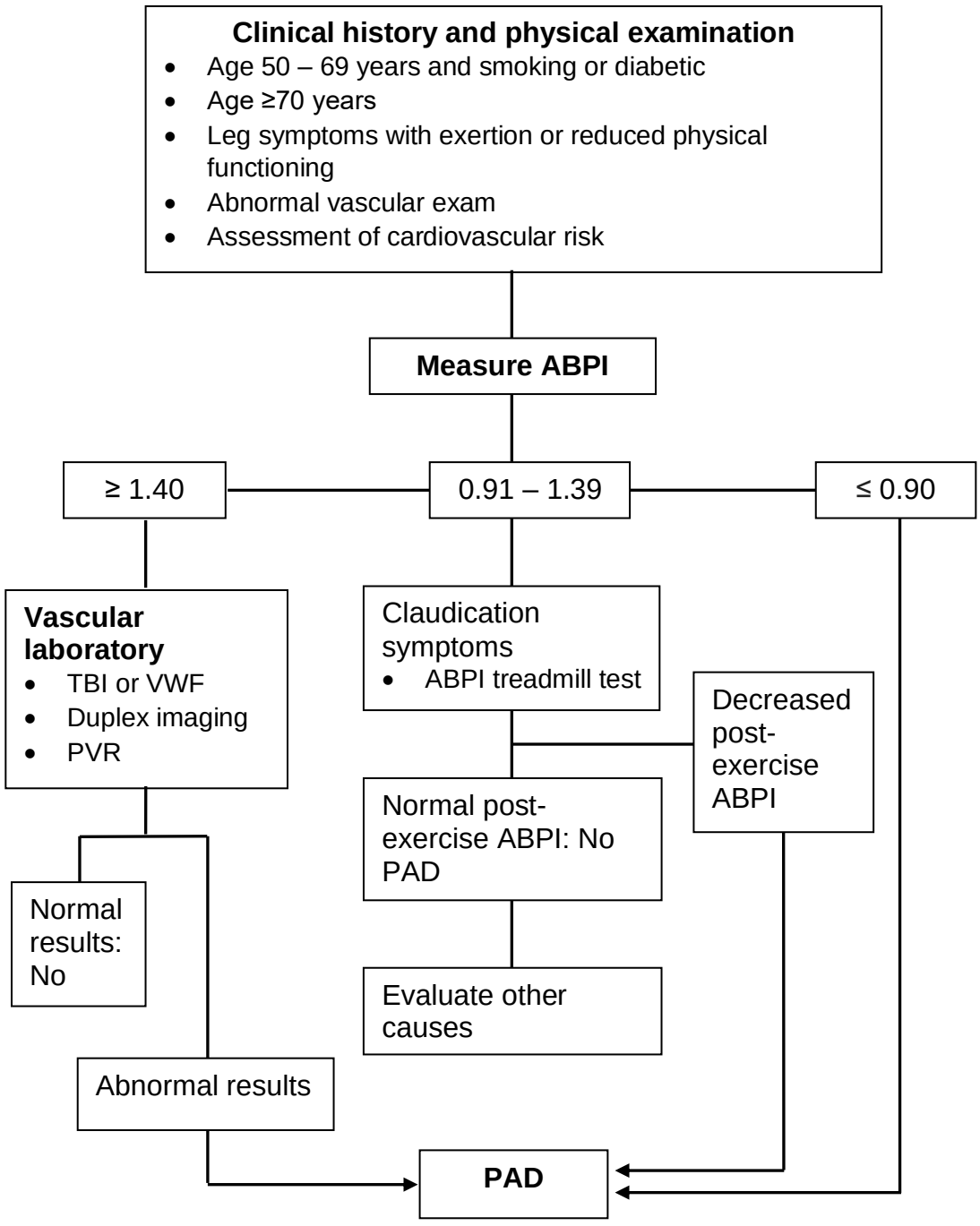


FIGURE 3: Diagnostic approach for PAD (Norgren et al., 2007).

ABPI – ankle-brachial pressure index; TBI – toe brachial index; VWF – velocity wave form; PVR – pulse volume recording; PAD – peripheral arterial disease.

TABLE 2: Interpretation of resting ABPI results (Aboyans et al., 2018).

ABPI	Interpretation
1.39 – 1.01	Normal
1.00 – 0.91	Borderline PAD
0.90 - 0.41	Mild to moderate PAD
< 0.40	Severe PAD

ABPI is the traditional and most common clinical measurement for the screening, diagnosis, and haemodynamic monitoring of PAD. ABPI measurement is defined as the ratio of the highest systolic ankle blood pressure of each leg (measured at the dorsalis pedis or anterior tibial artery) to the highest left or right systolic brachial blood pressure. A resting ABPI <0.90 has 75% sensitivity and 86% specificity to diagnose PAD, with a lower ABPI indicating greater hemodynamically significant atherosclerotic disease (Xu et al., 2013). Additionally, a reduced ABPI is independently associated with reduced lower-body function (Mcdermott et al., 2004) and increased risk of future cardiovascular events and mortality (Norgren et al., 2007). An ABPI greater ≥1.40 is considered falsely elevated and likely be indicative of vascular calcification causing the artery around the ankle to become non-compressible, often associated in patients with diabetes, renal insufficiency and advancing age. In this situation, toe systolic pressures, pulse volume recordings, transcutaneous oxygen measurements or vascular imaging can diagnose PAD (Norgren et al., 2007). Resting ABPI is limited in its detection of PAD as some lesions may not cause an altered pressure gradient at rest, though become haemodynamically significant during exercise. Therefore, if symptoms strongly suggest IC however resting ABPI is normal, the assessment of ABPI can be obtained before and after treadmill exercise to

confirm diagnosis of PAD. A post-exercise ankle systolic blood pressure decrease of >30 mmHg or a post-exercise ABPI decrease of >20% compared with resting ABPI is indicative of PAD (Aboyans et al., 2012).

2.1.5 Impact of PAD and IC on Exercise Performance

Patients with PAD have greater decline in physical function, lower physical activity, and higher rates of mobility loss than people without PAD (McDermott et al., 2010; Mcdermott et al., 2002; Mcdermott et al., 2001; McDermott et al., 2009; Mcdermott, et al., 2004). For example, lower ABPI was associated with slower walking velocity, poorer standing balance, and increased time to complete 5 chair stands compared with normal ABPI (**TABLE 3**).

TABLE 3: Percentage difference of lower body function assessments among women with PAD with ABPI <0.9 compared to women without PAD with ABPI of 0.9 – 1.5 (Mcdermott, et al., 2000).

	ABPI	
	< 0.5	**0.5 – 0.9**
Usual pace walking velocity	-22.4%	-14.3%
Fast-paced walking velocity	-21.9%	14.1%
Time for 5 chair stands	15.3%	12.5%
Standing balance	-20.6%	-21.1%

Walking performance, specifically maximal walking distance and walking speed is significantly impaired in PAD (Askew et al., 2005). Furthermore, patients with PAD (ABPI <0.9) covered significantly less distance (349.8 ± 65.1 m) in the 6-minute walk test (6MWT) compared to people without PAD (515 ± 96.4 m) (Dziubek et al., 2015). This is particularly important considering the association between the 6MWT and disease specific health-related QoL (HR-QoL) measures (**TABLE 4**); of which is reduced in patients with PAD (Harwood, Totty, et al., 2017). An impaired aerobic capacity and walking economy is observed in PAD, which contributes to reduced ability to sustain exercise under aerobic metabolism (Farah et al., 2015; Gardner et al., 2010). Patients with PAD have lower $\dot{V}O_2$ peak than non-PAD controls (PAD: 15.7 ± 3.7 $ml.kg^{-1} \cdot min^{-1}$; non-PAD: 24.8 ± 5.5 $ml.kg^{-1} \cdot min^{-1}$) (Askew et al., 2005). Patients with PAD also present with reduced muscle strength, with findings that show calf muscle strength to be 43% lower in PAD than in non-PAD controls (Askew et al., 2005; Garg et al., 2011; Hiatt et al., 2015). The reduction in strength was also positively correlated with peak walking time on treadmill ($r = 0.41$, $p < 0.005$).

TABLE 4: Correlation coefficients between objective measures of PAD severity and HR-QOL measures in 80 patients with PAD (Izquierdo-Porrera et al., 2005).

Disease specific HR-QOL measurement	ABPI	Time to maximal claudication	6MWT
Walking Impairment Questionnaire Score			
Distance walked	0.29†	0.42‡	0.45‡
Stair climbing	0.20	0.39†	0.40†
Speed walking	0.16	0.29†	0.24*
Generic quality of life measures			
Medical Outcomes Study Short-Form 36			
Physical functioning	0.42‡	0.43‡	0.48‡
Role-physical	0.26*	0.33†	0.39†
Bodily pain	0.30†	0.17	0.19
General health	0.15	0.23	0.28*
Role-emotional	0.03	0.14	0.10
Vitality	0.18	0.22	0.29*
Mental health	-0.02	0.27*	0.37†
Social functioning	0.09	0.21	0.14

* p <0.05; † p <0.01; ‡ p <0.001

Studies have repeatedly reported the association of daily physical activities with functional decline among patients with IC (Garg et al., 2010; Mcdermott, Greenland, Ferrucci, et al., 2002). Patients with IC have significantly lower physical activity behaviours than people without PAD when physical activity is objectively measured using a device-based measure such as an accelerometer. Over a 7-day period, people without PAD were shown to be twice as active as

patients with IC (Mcdermott et al., 2000). Indeed, exercise intolerance is the hallmark of IC, contributing to sedentary lifestyles. In some cases, patients with IC may restrict their physical activity or slow their walking speed to self-manage IC pain (McDermott et al., 2010). The consequence of continued restricted daily physical activities exacerbates infirmity and furthers functional decline through superimposed deconditioning of skeletal muscle and lower health related QoL.

2.1.6 Physiological Mechanisms of PAD Impact on Exercise Performance

Many pathophysiological processes contribute to the development and severity of PAD that is associated with physical function impairment and decline because of exposure to cardiovascular risk factors and inflammation (**FIGURE 4**) (Hamburg & Creager, 2017). Although the mechanisms causing physical function impairment and decline in PAD are not fully understood, research suggests that both impaired vasculature and skeletal muscle pathophysiologic changes contribute. The pathophysiological processes and their physiological consequence potentially affecting physical function are detailed in **TABLE 5**.

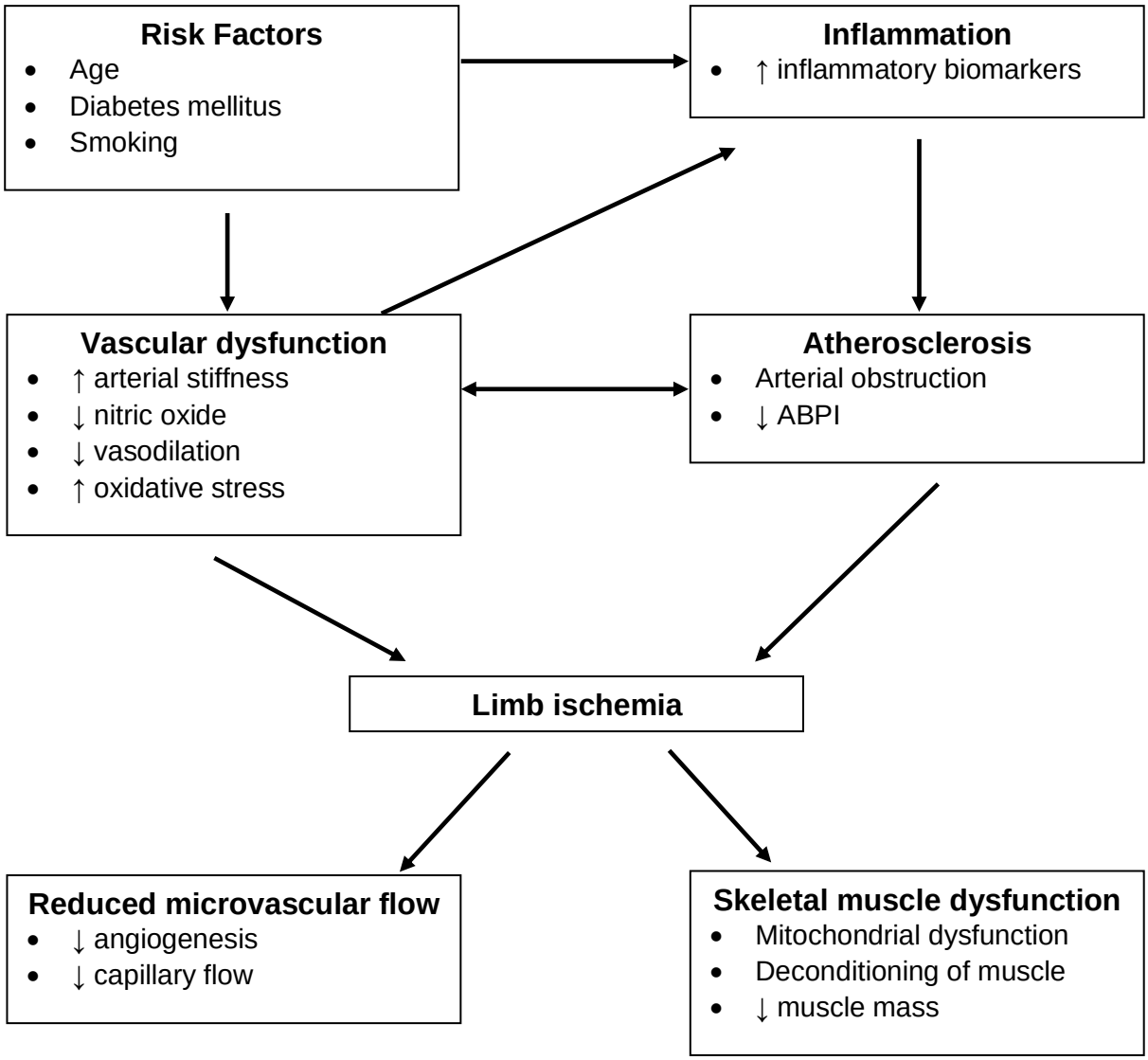


FIGURE 4: Pathophysiological process contributing to the development and severity of PAD and associated functional impairment and decline (Hamburg & Creager, 2017).

TABLE 5: Pathophysiological process to PAD and physiological consequences.

Pathophysiological Process	Consequence
Arterial obstruction	Reduced blood flow
Endothelial dysfunction	Decreased vasodilator function
	Increased arterial stiffness
	Impaired hyperaemic response
	Impaired arterial remodelling
	Increased inflammatory activation
Mitochondrial dysfunction	Impaired energy production
	Impaired oxygen utilisation
	Increased reactive oxygen species
	Reduced skeletal muscle content
	Adverse skeletal muscle remodelling
Inflammatory activation	Increased atherosclerotic progression

Within blood vessels, damage to endothelial cells initiates vessel wall inflammation, smooth muscle cell proliferation, fibrin formation and coagulation factors contributing to the development and clinical manifestation of atherosclerosis. A consequence of developing atherosclerotic plaque is inadequate perfusion with exercise. In healthy people during steady state exercise, heart rate and ventilatory oxygen uptake increases and stabilises to allow sufficient arterial circulation of oxygen and substrates to active skeletal muscle to match the metabolic demand of exercise (Wasserman, 1994). Optimising muscle blood flow during exercise to minimise the overall resistance to flow delivery to active muscle is dependent on vasodilation, an active process with several important vasoactive mediators (Boushel et al., 2002). Patients with

PAD present significant abnormalities in endothelium-dependent vasodilation that impedes the augmentation of blood flow with exercise (Coutinho et al., 2011; Walker et al., 2016); in conduit artery there is a significant blunted blood flow response to the onset of exercise that plateaus at flows well below that observed in healthy people (Bragadeesh et al., 2005). Furthermore, PAD is associated with reduced microvascular flow. Patients with PAD have shown to have a decreased skeletal muscle capillary density compared with healthy controls (Robbins et al., 2011a). This may be a result of inadequate angiogenesis and collateral formation as a response to chronic ischemia that may potentiate limb ischemia (Semenza, 2007). The relative area of type I fibres, the capillary-to-fibre ratio, capillary contacts with type I and II fibers, are positively correlated with exercise tolerance in a PVD sample but not controls (Askew et al., 2005).

Ischemia reperfusion is an important initiator of the subsequent changes in skeletal muscle structure and metabolic properties. Patients with PAD experience calf muscle reperfusion during rest, when blood supply increases sufficiently to meet calf muscle oxygen requirements. This phenomenon of ischemia–reperfusion generates reactive oxygen species, such as superoxide anion and hydrogen peroxide, that can damage muscle fibres, impair mitochondrial function, and promote apoptosis (Gillani et al., 2012; Pipinos et al., 2008). For example, in 92 patients with PAD whose left and right leg ABPI values differed by >0.20, computed tomography demonstrated that legs with more severe ischemia had 5% less calf muscle area and 9.5% higher fat content (Mcdermott et al., 2007). On muscle biopsy, there is greater muscle cell apoptosis and reduced type I fibre content (Askew et al., 2005; Mitchell et al., 2007). Selective fibre type switching

from type I (aerobic) to type II (glycolytic) fibres may impair skeletal muscle performance and has been associated with decreased exercise tolerance (Askew et al., 2005). Ischemia also damages peripheral nerve function, with evidence of poor nerve conductance in patients with severe PAD that further attenuates the ability to produce force (Garg et al., 2011).

Alterations in oxygen coupling and mitochondrial respiration is evident in PAD. In patients with PAD a profound prolongation of the kinetic rates of pulmonary oxygen consumption and tissue haemoglobin desaturation have been described at the onset of exercise relative to healthy, age-matched controls (Bauer et al., 2007). In the muscle tissue, mitochondrial mass is higher; however, there is lower activity of several mitochondrial complexes impeding ATP generation and enhancing reactive oxygen species production (Anderson et al., 2009; Pipinos et al., 2008). Phosphocreatine recovery rates is an indicator of mitochondrial function. Phosphocreatine was found to be inversely correlated with exercise treadmill time, supporting that mitochondrial dysfunction limits exercise performance in IC (Anderson et al., 2009; Pipinos et al., 2002). Notably, many patients with IC have slower phosphocreatine recovery rates compared to non-PAD muscle, though is not universally seen in patients. Interestingly, patients with normal mitochondrial indices showed a shorter recovery time from their IC pain compared with patients with abnormal mitochondrial indices (Pipinos et al., 2002)

Altered muscle metabolism also reflects reduced nutrient uptake related to systemic metabolic disturbances in patients with PAD. By evaluating skeletal muscle glucose uptake with dynamic positron emission tomography, it has been

shown that PAD patients with IC have calf muscle insulin resistance (Pande et al., 2011). Muscle lactate levels are also significantly increased in the skeletal muscle of patients with PAD as a result of incomplete oxidation of glucose (Barker et al., 2004).

Neurohumoral activation may impact exercise performance. The exercise pressure reflex responds to the onset of exercise and activates sympathetic nervous system, increasing HR, BP, myocardial contractility and peripheral vasoconstriction (Mccloskey & Mitchell, 1972). In PAD the exercise pressor reflex is exaggerated, and sympathetic nervous system over activates which significantly increases the blood pressure responses to exercise (Bakke et al., 2007). This causes vasoconstriction and reduces blood flow which can contribute to a reduction in walking and pain whilst walking (Baccelli et al., 1999).

2.1.7 Management and Treatment of IC

The clinical aim for patients with IC is to improve IC symptoms, improve exercise performance, improve QoL, and to prevent and delay the progression of atherosclerotic disease and adverse cardiovascular outcome (Kullo & Rooke, 2016). **FIGURE 5** depicts the overall management and treatment strategy for IC. Patients with IC and coexisting conditions present additional challenges in the overall strategy of treatment that are not presented.

The strategy begins with cardiovascular risk factor management, including nonpharmacological measures such as smoking cessation, healthy diet, weight loss and regular exercise and pharmacological measures such as anti-

hypertensive, lipid-lowering, and anti-thrombotic drugs (Piepoli et al., 2016). Patients with IC who are physically impaired, exercise therapy and in selected patients' pharmacotherapy would be employed to improve exercise performance (risk factor modification and anti-platelet therapies are indicated to decrease the risk of cardiovascular events) (Norgren et al., 2007). Failure to respond to exercise and/or drug therapies would lead to the consideration of revascularisation procedures.

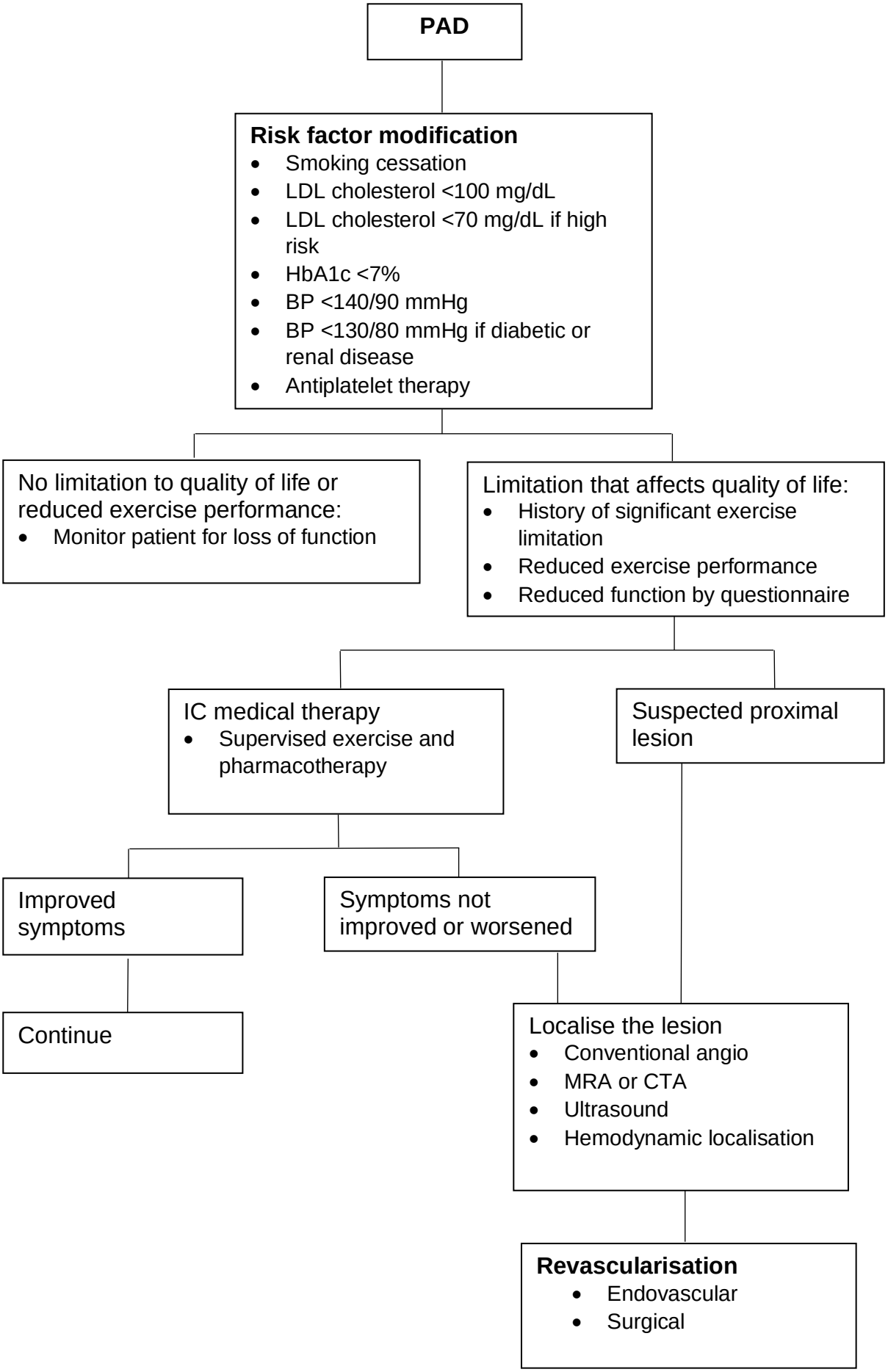


FIGURE 5: Overall management and treatment strategy for PAD (Gerhard-Herman et al., 2017).

2.1.8 Smoking Cessation

Tobacco smoking is a major risk factor for the development and progression of PAD and the most important modifiable risk factor (Chi & Jaff, 2008). Smoking has haematological effects such as increased blood viscosity, and promotion of endothelial dysfunction and platelet aggregation (Ambrose & Barua, 2004). Smoking cessation has been shown to be beneficial in reducing the risk for PAD progression in patients with IC, and cardiovascular events such as myocardial infarction and stroke (Lu & Creager, 2004). Following endovascular procedures, individuals who smoke >10 cigarettes daily are more likely to have restenosis (Schillinger et al., 2004). Similarly, those who stop smoking after lower-limb bypass surgery have improved outcomes compared with those who continue to smoke (Willigendael et al., 2005). Importantly, smoking cessation does not significantly improve maximum walking distance in patients with IC (Girolami et al., 1999). Therefore, smoking cessation must be combined with another treatment strategy to improve exercise performance.

2.1.9 Pharmacological Treatment

Pharmacological treatment for risk factor modification and reducing cardiovascular events risk are warranted in almost all PAD patients. This can include lipid control with a statin, blood pressure lowering with angiotensin converting enzyme inhibitor or angiotensin receptor blocker therapy; and blood glucose control (Conte & Vale, 2018). Statins can have a symptom benefit, resulting in walk distance improvement by 24% and 42% at 6 and 12 months (Aronow et al., 2010). Additionally, angiotensin converting enzyme inhibitor ramipril has demonstrated to improve walking distance, time, and subjective

walking measures (Aronow et al., 2010). Antiplatelet therapy with aspirin or clopidogrel has been shown to result in a 23% reduction in vascular events (Collaboration, 2002).

2.1.10 Revascularisation

Revascularisation (endovascular procedures, open arterial bypass, or both) occur in severe cases of PAD that do not respond to pharmacology or exercise, with significant disability due to IC, or with clinical symptoms of critical limb ischemia to prevent gangrene and limb amputation (Norgren et al., 2007). Few patients require invasive treatment when adhering to standard medical care (Conte et al., 2015). It is estimated that 10% to 15% of patients with critical limb ischemia require revascularisation (Leng et al., 1996).

2.1.11 Exercise Treatment

Walk training and physical activity are particularly important in the treatment of IC (Serracino-inglott et al., 2007). Structured walking is the most significant non-medical treatment for IC along with treatment for cardiovascular risk factors. Current treatment guidelines for IC recommend walking exercise as the first-line treatment recommending intermittent walking until moderate to maximal claudication pain three times a week for approximately 40 minutes per session for at least 6 months, along with other modes of aerobic exercise and resistance training as an adjunct treatment for the condition (Conte et al., 2015; Gerhard-Herman et al., 2017). Structured and supervised walking training has been shown to be produce greater outcomes non-supervised walking (Conte & Vale, 2018).

Randomised controlled clinical trials have consistently demonstrated that supervised treadmill exercise produces clinically relevant increases in pain free and maximal treadmill walking distance in patients with IC. For example, a meta-analysis from the Cochrane database (Lane et al., 2017) involving 32 critically evaluated randomised controlled trials of walking exercise treatment that randomised a total of 1,835 patients with IC reported an overall improvement in peak walking distance of 120 m [95% CI; 50.8 to 189.9] ($p < 0.01$) and pain-free walking distance of 82 m [95% CI; 71.7 to 92.5] ($p < 0.01$) compared to a non-exercise control group. These findings are consistent with an earlier meta-analysis that reported supervised treadmill exercise was associated with 180 m of improvement in maximal walking distance and 128 m of improvement in pain-free walking distance, compared to a non-exercise control group (Fakhry et al., 2012). Walking exercise treatment for 12 to 24 weeks improves waking performance which can improve QoL and physical activity levels that result in reducing risk factors (Serracino-inglott et al., 2007).

Most exercise training trials in patients with PAD have used walking as the exercise training mode, as well as the primary outcome measure. As a result, walking predominates in the exercise prescription even though the mechanisms by which exercise performance improves are unclear. Critically, there are several potential issues with walking exercise for patients with IC. Firstly, patients with IC are limited in their ability to walk and the pain encountered during walking may cause anxieties such as, fear of pain and fear of fatiguing (Binnie et al., 1999). As a result, adherence to walking can be difficult for many patients with IC, and this is reflected in the relatively high drop-out rates. For instance, of 1,541

potential patients with IC eligible for inclusion in supervised exercise programmes, 769 (50%) reported lack of interest or simply refused participation in supervised exercise (Harwood et al., 2016).

Whilst walking exercise is the gold standard prescription for IC and improves walking performance, it is not the optimal training modality to improve peak $\dot{V}O_2$, functional outcomes (Parmenter et al., 2015), muscle mass or muscle strength (McDermott et al., 2009; Vun et al., 2016). Other aerobic modes of exercise training and resistance exercise are recommended to be performed alongside walking exercise to improve cardiovascular outcomes and address PAD related muscle myopathy (Gerhard-Herman et al., 2017).

Arm ergometry is a claudication pain free aerobic exercise mode for patients with IC which allows a greater exercise volume to be performed compared to walking exercise which has shown to increase pain free walking (~50%) and walking distance (~30%) (Tew et al., 2019; Zwierska et al., 2005). Arm ergometry has shown to provide a stimulus sufficient to improve peak $\dot{V}O_2$ that enables improved exercise performance (Parmenter et al., 2015). However, arm ergometry does not address lower-extremity muscular maladaptation caused from PAD.

Resistance training is an important element to exercise treatment in patients with IC to address lower-extremity muscle weakness (McDermott et al., 2012) and can be used exclusively or adjunct to walking exercise. A meta-analysis concludes that resistance training improves lower limb strength and both flat ground and graded walking distance in patients with IC but not to the same extent as walking

exercise (Parmenter et al., 2019). However, resistance training is important to increase muscle mass (McGuigan et al., 2001) and muscle strength (Parmenter et al., 2013; Ritti-Dias et al., 2010), characteristics that are affected in patients with IC (McDermott et al., 2012). This meta-analysis included studies showing a strong association between changes in strength levels and changes in walking capacity after resistance training (Parmenter et al., 2013; Ritti-Dias et al., 2010) suggesting that strength gains lead to greater muscle fibre recruitment during walking, thereby reducing the energy cost of walking.

2.1.12 Potential Local Mechanisms of Improved Exercise Performance Following Exercise Treatment

The potential mechanisms of exercise to improve claudication symptoms are not completely clear. Virtually all trials that have evaluated the importance of exercise training in patients with IC have exhibited an increase in exercise tolerance (Levine, 2018), but it is noted that exercise has not shown to affect ABPI and haemodynamics (Paramenter et al., 2010). A variety of adaptive mechanisms in the lower limb muscles have been suggested, including improved endothelial vasodilator function, skeletal muscle mitochondrial metabolism, muscle architecture, and muscle strength and endurance (Harwood, Cayton, et al., 2016).

Patients with IC have an impaired flow mediated dilatation (FMD) in comparison to age matched healthy controls (Brendle et al., 2001). FMD is the gold standard assessment of endothelial function. The endothelium regulates the physiological balance elaborating a variety of paracrine factors locally in the vasculature, such

as vascular tone and blood flow via production of nitric oxide (NO) by endothelial NO synthase (Cahill & Redmond, 2016). In PAD, NO release is degraded by reactive oxygen species which impairs vascular smooth muscle cells relaxation and vasodilation. Exercise programmes significantly improves flow mediated dilatation in patients with IC (Brendle et al., 2001). This is potential due to an increased laminar flow with exercise upregulating endothelial NO synthase phosphorylation and antioxidant protection, which appears more effective during aerobic type exercise than resistance exercise (Mcdermott et al., 2009).

Patients with IC have an increase mitochondrial density and activity compared to healthy controls to compensate for the higher metabolic demand on skeletal muscle (Pipinos et al., 2006). Additionally, the ischemia and inflammatory response in PAD results in both morphological alterations and DNA damage to the mitochondria (Brass & Hiatt, 2000). The administration of exercise training improves mitochondrial capacity, through increased mitochondrial content (Schaardenburgh et al., 2017). Additionally, pentoxifylline also improves mitochondrial function exclusive of change in blood flow and therefore, is most likely due to a change in intrinsic mitochondrial oxidative activity (Pipinos et al., 2002).

Calf muscle morphology in patients with IC comprises a higher fat percentage, lower muscle cross sectional area and lower proportion of Type 1 muscle fibres (Askew et al., 2005). Additionally, the number of capillaries per muscle fibre is reduced, markers of apoptosis is increased, and glucose uptake is impaired resulting in atrophy (Mitchell et al., 2007; Mockford et al., 2014; Pande et al.,

2011; Robbins et al., 2011). Exercise programmes improve mitochondrial content contributing to increased exercise performance and programmes that include resistance exercise demonstrate an increase in muscle size, capillary density, and improvement in muscular function (Crowther et al., 2012; McGuigan et al., 2001; Wang et al., 2009). Leg strength is significantly increased following strength training programmes leads to an improved walking economy and has shown to improve 6-minute walk test (6MWT) distance by ~8%, (p <0.08) after 12 to 24 weeks (Parmenter et al., 2019; Wang et al., 2010) and there is a strong association between change in plantar flexor muscle strength and walking ability (Mcdermott et al., 2009; McGuigan et al., 2001).

2.1.13 Patient Experiences of Exercise

The primary disadvantage of supervised exercise programmes for IC patients are the poor uptake, adherence, and dropout rates. Data from a Vascular Surgery Unit that offered a supervised exercise programme consisting of 3 sessions a week for 12 weeks as secondary care showed from 422 patients eligible to undertake the exercise programme 92 patients (22%) agreed to enrol. Of the 92 patients who took part in the exercise programme, 38 patients (41%) fully completed, and 38 patients (41%) actively withdrew (Harwood et al., 2017).

Data from qualitative studies show patients preconceptions to exercise are mixed in IC patients (Gorely et al., 2015; Harwood et al., 2017). Many patients recognise the benefits of exercise to cardio-respiratory physiology, body-composition, mobility, and mental health; however, many patients are uncertain how walking

that causes pain can reduce IC related symptoms, and anxious that exercise could worsen their condition (Gorely et al., 2015).

Many patients that engaged with the supervised exercise programme report positively, expressing an enjoyment from the social aspect of attending sessions and motivation to exercise from experiencing improvements in walking performance (Harwood et al., 2017). Many barriers to exercise are identified. Pain while exercising is seen as the primary barrier, followed by a lack of motivation to exercise from modes of exercise that are not interesting, a lack of time where other commitments such as family care take priority, a fear of worsening the condition, and a lack of confidence to exercise enough to gain a benefit (Gorely et al., 2015). Many patients described the burden of attending the supervised exercise programme such as time of sessions that are inconvenient to them, trouble to access transport and the cost of transport (Harwood et al., 2017).

2.1.14 Rationale for Exercise as an Adjunct Treatment for Intermittent Claudication

Reduced exercise performance is a hallmark of IC. The overall goal in treating exercise limitation from IC is to improve exercise performance and functional status to increase QoL. Therefore, strategies that improve walking ability are the basis for successful treatment. Exercise programmes are part of primary treatment for IC, with a well-established benefit after a typical 12-week exercise programme (Lane et al., 2017). Exercise training directly modifies several pathophysiological mechanisms in PAD, including improved endothelial function,

skeletal muscle metabolism, and muscle architecture, enabling enhanced exercise performance (Harwood et al., 2016). Walking to moderate to maximal claudication pain is the recommended modality for IC (Gerhard-Herman et al., 2017). However, the most common barrier to exercising is patients with IC is related to pain experienced when walking (Gorely et al., 2015). As such, exercise programmes have poor uptake and adherence in IC patients (Harwood et al., 2016). Therefore, the prescription of an exercise programme must be focused on achieving the relevant clinical outcomes of improved physical function, predominately walking performance. The exercise should provide a stimulus that targets specific muscular adaptations to address maladaptation from PAD, namely improved skeletal muscle metabolism, muscle capillary density, endothelial function, and muscle architecture. There should also be an awareness of the potential negative psychological consequences of exercising that provokes high levels of claudication pain. Therefore, prospective modes of exercise should target lower-extremity muscle, be similarly as effective as walking exercise and limit the amount of claudication pain experienced whilst exercising.

2.2.1 Blood Flow Restriction Resistance Exercise

BFR-RE has received substantial attention in scientific literature during the last decade as a prospective alternative modality to promote beneficial muscular adaptations in healthy, clinical, and athletic populations (Centner et al., 2019; Grønfeldt et al., 2020; Hughes et al., 2017; Loenneke, Wilson, et al., 2012; Scott et al., 2016; Slysz et al., 2016). The general principle of the BFR-RE technique is that an external compression, typically using a pneumatic tourniquet cuff, is applied around the most proximal region of the exercising limb whilst lifting low

loads (20 - 40% 1RM) (Patterson et al., 2019). When the cuff is inflated, there is gradual mechanical compression of all soft tissues underneath the cuff reducing vascular diameter. This causes partial restriction of arterial blood flow to structures distal to the cuff but more severely, reduces/occludes venous outflow from under the cuff (Mouser et al., 2017).

The acute response during BFR-RE is turbulent arterial blood flow, reduced intramuscular oxygen delivery, decreased venous clearance of metabolites and blood pooling within the capillaries, causing exaggerated levels of metabolic stress and increasing muscle fibre recruitment during exercise (Suga et al., 2009). When the cuff is released, reperfusion and shear stress initiate a vasodilatory and/or enhance blood flow response (Patterson & Ferguson, 2010).

Guidelines for effective prescription of resistance exercise recommend loads of ≥60% 1RM are required to increase strength and promote hypertrophy (Gardner et al., 2018). However, BFR-RE has frequently shown to increase strength, muscle size and muscular endurance despite the use of low loads (Centner et al., 2019; Fahs et al., 2015; Manimmanakorn et al., 2013; Patterson & Ferguson, 2010). Notably, the increase in muscle volume and cross-sectional area following BFR-RE are comparable to traditional resistance exercise but increases in strength are to a lesser extent (Centner et al., 2019; Grønfeldt et al., 2020; Lixandrão et al., 2018), this is despite much lower loads. Furthermore, when BFR-RE is compared with matched volume-load resistance exercise without BFR, much lower exercise volume and durations are required to produce the same training stimulus for muscular adaptations (Fahs et al., 2015). Therefore, BFR-

RE appears to be a viable, time-efficient and efficacious alternative to traditional resistance exercise for muscular development and has been advocated typically for populations where traditional resistance exercise may not be feasible or contraindicated, such as older or elderly adults (Centner et al., 2019) and rehabilitation patients (Hughes et al., 2017).

2.2.2 BFR-RE Protocol

The method BFR-RE is applied can have a substantial impact into many of the acute and chronic responses. In particular, the level of restrictive cuff pressure and the volume-load (sets, reps and load). It is important to understand the influence of these factors in order to safely prescribe the technique to high-risk individuals and improve the likelihood that muscular adaptations will occur from a period of training.

Determining the appropriate restrictive cuff pressure for an individual participating in BFR-RE is crucial. The restrictive cuff pressure will determine the degree of BFR experienced for the individual and will affect neuromuscular, haemodynamic, metabolic and perceptual responses during the exercise and the subsequent training stimulus (Fahs et al., 2012; Kacin & Strazar, 2011; McEwen et al., 2019; Patterson et al., 2019; Sumide et al., 2009). A difficulty for researchers has been selecting a method to prescribe the restrictive cuff pressure that provides an equal degree of BFR between participants to achieve consistent responses from the exercise.

At an absolute restrictive cuff pressure, the degree of BFR experienced by the individual is predominantly subject to the width of the restrictive cuff and participant characteristics (Hunt, Stodart, & Ferguson, 2016; Jessee et al., 2016; Loenneke et al., 2012). Wider restrictive cuffs transmit pressure through soft tissues differently than narrow restrictive cuffs and require less pressure to reduce arterial blood flow. For example, the pressure required to occlude arterial blood flow in the legs in young people (22 ± 3 years) with a 13.5 cm wide restrictive cuff was 144 ± 17 mmHg compared to 235 ± 42 mmHg required using a 5 cm wide restrictive cuff (Loenneke et al., 2012). Participant characteristics are an equally important consideration. Limb circumference has previously been described as the largest determinant of complete arterial occlusion pressures for thighs (Loenneke et al., 2012). Larger limbs require higher restrictive cuff pressures to reach the same deep tissue pressure compared with smaller limbs. Although it is argued limb circumference (r = 0.34) has limited impact on the cuff pressure required for partial blood flow restriction in the thighs and systolic blood pressure (r = 0.49), diastolic blood pressure (r = 0.57), mean arterial pressure (r = 0.58) are stronger independent predictors (Hunt et al., 2016).

Many early BFR studies have applied a standard restrictive cuff pressure, independent of individual differences and often chosen from previous literature using different sized restrictive cuffs (Abe et al., 2009; Evans, Vance, & Brown, 2010; Kacin & Strazar, 2011; Madarame et al., 2008; Sakuraba & Ishikawa, 2009; Takarada et al., 2000; Yasuda, Loenneke, Thiebaud, & Abe, 2012). If investigations ignore restrictive cuff size and individual differences in the prescription of restrictive cuff pressure, the degree of BFR may be different

between the participants (Hunt et al., 2016), may influence the effectiveness of BFR (Counts et al., 2016) and individuals experience evidenced by changes in perception of exertion and pain during exercise (Loenneke et al., 2015) but will become a safety concern (Loenneke et al., 2013; Patterson et al., 2019).

To account for restrictive cuff and individual differences, it has been suggested prescribing restrictive cuff pressure as a percentage of arterial occlusion pressure [the amount of pressure required to cease blood flow to a limb; (AOP)] (McEwen et al., 2019; Patterson et al., 2017). This is achieved by inflating the cuff in its position used during exercise up to the point where blood flow ceases (100% AOP) and using a percentage of that pressure (e.g. 40–80% of AOP) during BFR-RE. It is noted that applying a relative restrictive cuff pressure of 40% AOP does not result in a 40% reduction in blood flow (Mouser et al., 2017), and it is unknown the variance of reduction in blood flow between individuals at a set relative restrictive cuff pressure. Though, applying pressure as a percentage of AOP through three different sized restrictive cuffs has shown to produce similar change in resting blood flow (Mouser et al., 2017). There is a clear inverse relationship between cuff width and AOP (Jessee et al., 2016; Mouser et al., 2017). Although larger cuffs require less pressure to achieve a desired percentage of AOP, this does not necessarily equate to a safer stimulus but is evidence that applying a wide cuff compared with a narrow cuff increases the distance of pressure being applied to the tissue. Therefore, within the tissue, blood vessels are compressed over a longer distance with a wide cuff versus a narrow cuff, which in turn will create a greater resistance to blood flow (Jessee et al., 2016; Mouser et al., 2017).

The effectiveness of exercise with BFR to produce beneficial adaptations in skeletal muscle is determined by the degree of BFR that balances the level of muscle activation and fatigue (contractile/metabolic impairment) during exercise. With an increase in restrictive cuff pressure, in turn increases the neuromuscular, haemodynamic, metabolic, and perceptual response of exertion and pain during exercise with BFR but not necessarily optimising the longer-term (Fahs et al., 2012; Kacin & Strazar, 2011; McEwen et al., 2019; Patterson et al., 2019; Sumide et al., 2009). This has caused difficulty for practitioners using BFR for clients/patients to determine a restrictive cuff pressure that produces a beneficial muscular adaptation from exercise which is tolerable. The optimal restrictive cuff pressure is not known though it has been suggested that the effect of exercise with BFR may represent a hormesis relationship (Loenneke et al., 2014). Hormesis is traditionally defined as a theoretical phenomenon of dose-response relationships in which something that produces harmful biological effects at moderate to high doses may produce beneficial effects at low doses. In the case of BFR-RE, it may be that increasing the degree of BFR improves the muscular adaptation until a critical point where further increase in pressure may be ineffective in augmenting the skeletal muscle response, exaggerate the pain to exercise and increase the risk of injury to BFR-RE (**FIGURE 6**).

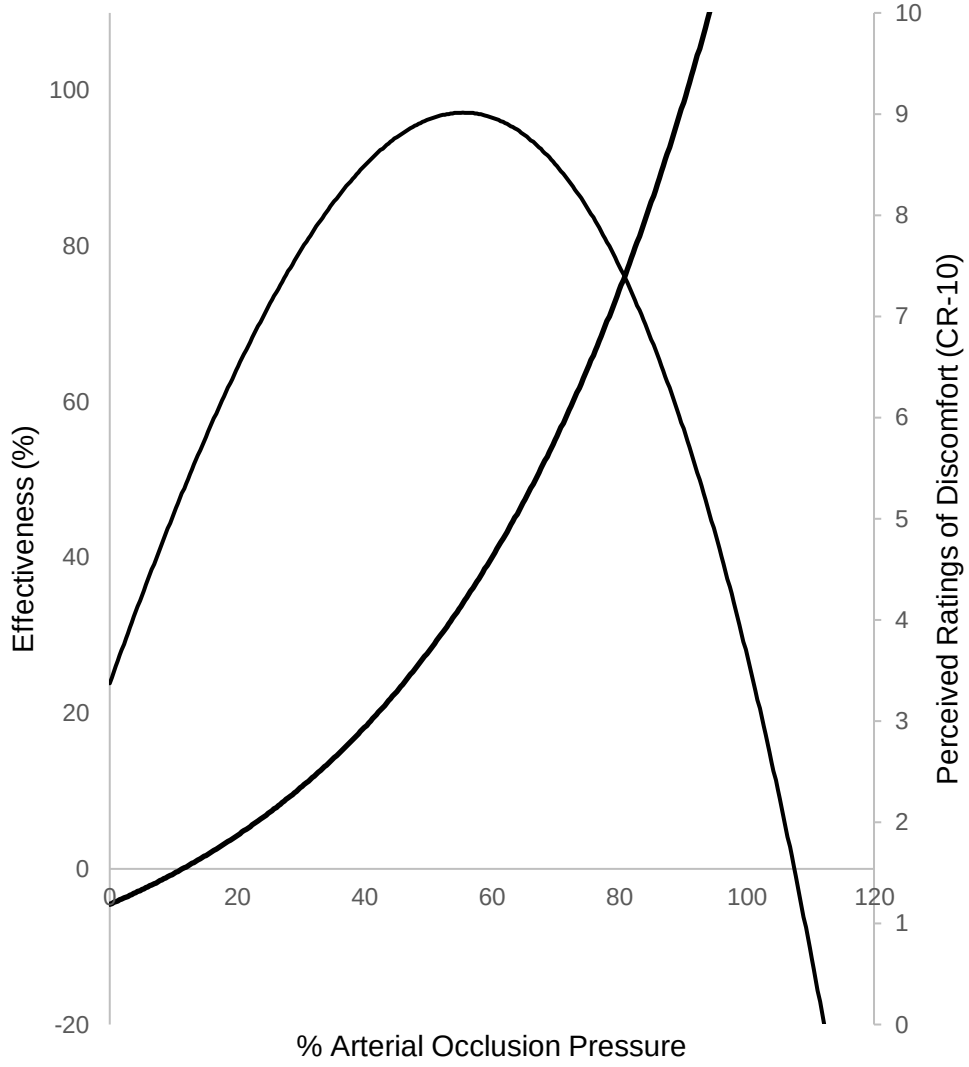


FIGURE 6: A theoretical diagram demonstrating the proposed relationship between the percentage of arterial occlusion pressure, the effectiveness to produce muscular adaptation and the perception of discomfort during exercise.

Low restrictive cuff pressures (<30% AOP) are unlikely to augment a muscular/metabolic response sufficient to produce a worthwhile training stimulus due to not effectively occluding venous blood to cause blood pooling. As such, little research exists applying these low pressures. Conversely, high restrictive cuff pressures (≥80% AOP) and complete arterial occlusion (≥100% AOP) can

limit the tolerable duration of exercise (Cook et al., 2007; Yasuda et al., 2008) and result in a decrement in muscular response reducing the effectiveness of BFR-RE as achieving a high exercise volume appears crucial in potential mediating factor for skeletal muscle hypertrophy (Burd et al., 2010) and vascular remodelling (Prior et al., 2003). The efficacy of BFR-RE has a broad window of effectiveness which seems to occur at moderate restrictive pressures (40% - 80% AOP) with the suppression of venous outflow (causing pooling of the blood) and partial but not complete reduction in arterial inflow (Cook et al., 2007; Evans et al., 2010; Fahs et al., 2014; Karabulut et al., 2010; Kim et al., 2009; Patterson & Ferguson, 2010; Suga et al., 2010; Takada et al., 2012). Therefore, the appropriate prescription of restrictive cuff pressure will likely be determined in consideration of the applied population group that considers a worthwhile degree of BFR and an acceptable level of pain experienced.

BFR-RE uses a low exercise load (20 – 40% 1RM) and high exercise volume (≈ 75 repetitions) to cause significant metabolic stress within muscle leading to recruitment of larger motor units which would not be expected under normal conditions **(TABLE 6).**

TABLE 6: Recommended guidelines for BFR-RE protocol including restrictive cuff details (Patterson et al., 2019).

Exercise Protocol	**Recommended Guidelines**
Frequency	2 – 3 times a week for >3 weeks
Load	20 – 40% 1RM
Volume	3 – 4 sets (75 reps, 30 x 15 x 15 (x15 or failure [optional])
Rest period between sets	30 – 60 s
Execution speed	1 – 2 s (concentric and eccentric)
Restrictive Cuff	
Restrictive cuff pressure	40 – 80% AOP
Restrictive cuff Width	5 cm (small), 10 – 12 cm (medium), 17 – 18 cm (large)
Restriction time	5 – 10 min per exercise (reperfusion between exercises)
Restriction form	Continuous throughout exercise or intermittent between sets

BFR-RE has consistently shown to be effective in augmenting changes in muscle strength and size in young (Slysz et al., 2016) and older adults (Centner et al., 2019), though the degree of effect varies. This undoubtably will be influenced by age, sex, training status, baseline strength and muscular size. But equally likely due to inconsistencies in exercise protocols used.

Determining the resistance exercise load will be influenced by the prescription of restrictive cuff pressure and in consideration of the desired training effect. For example, a study investigating the effects of different resistance exercise protocols found an augmented hypertrophy response from resistance exercise at 20% 1RM from an increase in restrictive cuff pressure from 40% to 80% AOP but not at exercise loads of 40% 1RM (Lixandrão et al., 2015). In the same study, it

was demonstrated that strength response did not alter despite modulation in restrictive cuff pressure or exercise intensity.

In the BFR literature, a frequently used set and repetition scheme exists of 75 repetitions across four sets of exercises with 30 repetitions in the first set and 15 repetitions in each subsequent set which has frequently shown effective (Karabulut et al., 2010; Madarame et al., 2008; Yasuda et al., 2012). This protocol was first developed anecdotally by Dr. Yoshiaki Sato in Japan, with the theory of encouraging blood pooling and metabolic stress with 30 repetitions in the first set that is either maintained or progressively increased by subsequent sets of 15 repetitions. This protocol was used in the first BFR studies (Takarada et al., 2000, 2002). It is also common that sets may be performed to concentric failure during BFR-RE (Manini et al., 2012; Ogasawara et al., 2013; Takarada et al., 2002). Though it is argued that exercise to failure does not augment a muscular adaptation response despite large increases in ratings of perceived exertion (RPE) and pain (Sieljacks et al., 2019). Also, training interventions of lower volume (4 x 15 repetitions) have also shown significant increases in muscle strength and size (Lixandrão et al., 2015).

Both single-joint and multi-joint resistance exercises are frequently employed with BFR, and although much of the focus is on the musculature distal to the cuff, synergist muscles that are not restricted also appear to benefit from the addition of BFR (Abe et al., 2006; Dankel et al., 2018). It is unclear exactly how this occurs, but a common theory is that the unrestricted synergist muscles are recruited to a greater extent in order to compensate for the reduced function of the restricted

muscles. This is supported by the findings of increased EMG activity in the pectoralis major muscle during bench press with BFR cuffs placed around the upper arms (Yasuda et al., 2010). This acute increase in EMG activity appeared to align the chronic increases in muscle thickness of the pectoralis major muscle, with no change reported in the unrestricted control condition. Of interest, the addition of BFR to bench press training appeared to perturb the typical ratio of muscular development that is seen with high-load resistance exercise. That is, greater increases in the CSA of the triceps brachii were noted in proportion to the CSA increases in the pectoralis major muscle (correlation coefficient of 0.7 vs 0.54 respectively). Therefore, it should be noted that chronic use of BFR with multi-joint exercises may bias the development of hypertrophy for synergist musculature over the prime mover. Differences between multi-joint and single joint have not been investigated. However, may influence the perceptual and physiological response that could impact the practitioners' decisions for protocol design.

2.2.3 Acute Haemodynamic Response to BFR-RE

The application of BFR subsequently compresses the conduit artery and disturbs the haemodynamic profile with increased shear stress (**FIGURE 7**). Following cuff inflation, retrograde shear rate increases in the absence of changes to antegrade shear rate, which increases in a dose-dependent response to the level of external pressure applied (Thijssen et al., 2009; Tinken et al., 2009). When exercising, the retrograde shear rate may decrease though the antegrade flow is likely to remain suppressed, which may impair endothelial function post exercise (Thijssen et al.,

2009). Under cuff placement, intramuscular pressure is increased, reducing artery diameter which may expose the artery walls to increased shear stress.

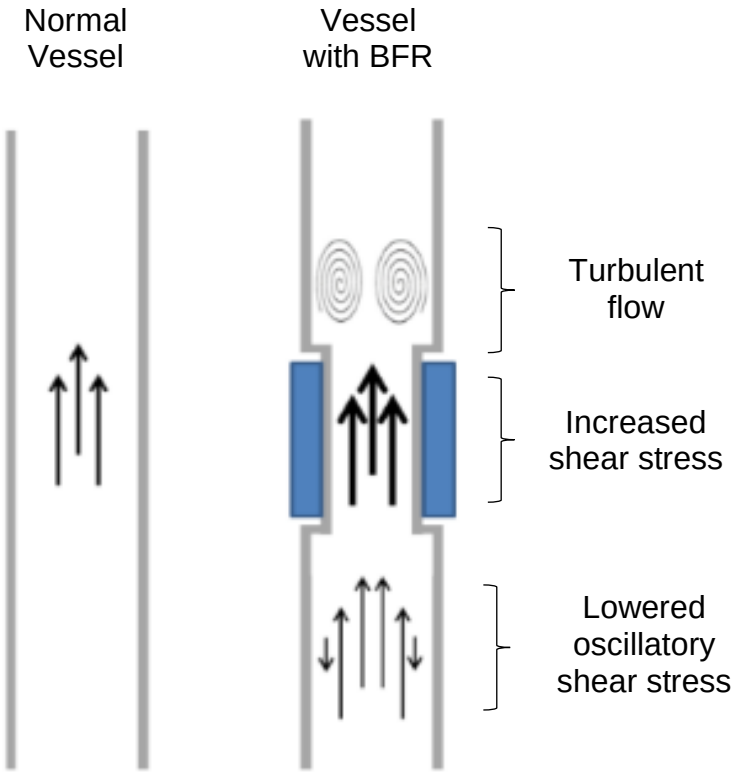


FIGURE 7: A schematic representation of the proposed haemodynamic response to BFR in the conduit artery. Adapted from (Chiu & Chien, 2011)

Immediately distal to the cuff there is a disturbed region of flow with reciprocating shear stress. This oscillatory shear profile distal of the cuff may augment endothelial NO release (Green et al., 2005). In addition, oscillatory shear conditions can increase adhesion molecules on the endothelial cells (Chappell et al., 1998; Hsiai et al., 2003) activating a local inflammatory response which is involved in the initial stages of both arterial remodelling (expansive remodelling)

and atherogenesis (constrictive remodelling) (Silver & Vita, 2006). However, prolonged exposure of >20-min to disturbed flow may increase ROS production, endothelial injury and impaired FMD (Jenkins et al., 2013; Rakobowchuk et al., 2013).

Following cuff deflation, the conduit artery is exposed to reactive hyperaemia increasing shear stress mediated NO release (Dakak et al., 1998). An increase in blood flow post BFR-RE can remain elevated 2-fold above rest for approximately an hour, demonstrating the prolonged effects of the shear stimulus (Gundermann et al., 2012).

2.2.4 Acute Muscle Oxygenation and Metabolic Stress Response to BFR-RE

The aim of the external compression is to limit arterial inflow and occlude venous return during exercise. This leads to tissue hypoxia, deprivation of nutrients and suppressed clearance of metabolic by-products (Tanimoto et al., 2005).

The enhanced and prolonged decrease in muscle oxygen levels during BFR-RE has been confirmed with near infrared spectroscopy measures (Tanimoto et al., 2005), which indicates a dose-response manner with the level of restriction pressure applied at rest (Karabulut et al., 2011). The reduced muscle oxygenation observed during BFR-RE may be lower than that observed during low load and high load resistance exercise without BFR (Corvino et al., 2017; Downs et al., 2014; Ganesan et al., 2015). For example, Downs et al., (2014) observed reduced thigh muscle oxygen saturation by 35% and 20% when leg press

exercise was performed to task failure at 20% and 80% of 1-RM, respectively, compared to reduced muscle oxygen saturation by approximately 50% when BFR was applied during the same exercise at 20% of 1-RM. The level of hypoxia is sustained provided the restrictive cuff pressure is maintained (Downs et al., 2014; Ganesan et al., 2015).

During BFR-RE, prolonged decrease in muscle oxygen enhanced metabolic perturbations in the working muscle of increased phosphocreatine depletion, inorganic phosphate production and decreasing muscle pH (Suga et al., 2009) and augmented lactate acid response (Reeves et al., 2006; Sato, 2005; Takarada et al., 2000). The metabolic perturbations observed may be of the same magnitude as resistance exercise performed with high loads (65-80% 1RM) (Neto et al., 2017; Poton & Polito, 2016). BFR-RE has shown to potentiate the expression of transcriptional responses VEGF, PGC-1α and eNOS mRNA, while up-regulating VEGFR-2 and HIF-1α mRNA, suggesting a targeted angiogenic response which is likely mediated through enhanced metabolic, ischemic and shear stress stimuli (Ferguson et al., 2018).

2.2.5 Acute Neuromuscular Response to BFR-RE

The size principle states motor units are recruited in order of their size, depending on the contraction intensity (Henneman, 1957). Therefore, small motor units comprised of type I muscle fibres are recruited first, and with a greater degree of force/velocity, larger motor units with type II muscle fibres are increasingly recruited.

To recruit higher threshold motor units, typically higher loading conditions (70-100% 1RM) are required. Under conditions of limit oxygen availability (such as under muscular fatigue or hypoxia), lower loads producing low contractile intensities can also recruit higher threshold motor units (Wernbom & Aagaard, 2020). This typically occurs when the oxygen-dependent type I fibres fatigue and cannot maintain muscular contraction, larger type II fibres that are better suited to anaerobic environments are recruited. BFR-RE can recruit high threshold motor units despite low loads (Fatela et al., 2019).

Data derived from studies investigating glycogen and phosphocreatine levels in muscles post BFR-RE are consistent with the order of motor unit recruitment units (Wernbom & Aagaard, 2020). The splitting of inorganic phosphate (which represents recruitment of higher threshold motor units), assessed via magnetic resonance spectroscopy, occurred in a similar percentage during BFR-RE and traditional high-load resistance exercise (Suga et al., 2012). Furthermore, phosphocreatine levels are reduced (89%) in fast twitch fibres with BFR-RE. Glycogen content following BFR-RE has shown to be reduced by 55% and 39% in the type I and type II fibres respectively. Collectively suggesting the recruitment of fast twitch muscles fibres with BFR-RE. Although type II fibres are recruited with BFR-RE, type I fibres are used to a greater extent (Wernbom & Aagaard, 2020).

2.2.6 Acute Cardiovascular Response to BFR-RE

The acute cardiovascular to exercise is coordinated by the autonomic nervous system, which redirects blood flow from inactive vascular beds (e.g. splanchnic)

to the active skeletal muscle (Cristina-Oliveira et al., 2020). Mechanical and chemical receptors within skeletal muscle relay information back to cardiovascular control areas in the brainstem through the exercise pressor reflex (Secher & Amann, 2012). During resistance exercise, blood pressure response increases in line with the mass of skeletal muscle recruited for the action. During BFR-RE, the cardiovascular response may be exaggerated by the acidic intramuscular environment activating the chemical receptors, through the muscle metaboreflex (Cristina-Oliveira et al., 2020). In addition, the reduction in venous return elicits a reduction in stroke volume, which may prompt a compensatory increase in HR to maintain cardiac output (Neto et al., 2017).

When matched for the same volume-load, BFR-RE typically elicits slightly higher acute increases in HR, blood pressures, and cardiac output, with reductions in stroke volume. However, when exercise is performed until muscle failure, these acute hemodynamic responses are similar (Neto et al., 2017). However, many studies conclude similar cardiovascular responses between BFR-RE and hihg load resistance exercise (May et al., 2017; Staunton et al., 2015) and in some cases lower for BFR-RE (Downs et al., 2014; Poton & Polito, 2016). This is an important consideration given that increased muscle strength and mass through BFR-RE in conjunction with a reduction in exercising cardiovascular demand, may alleviate some of the risk associated with high load resistance exercise for populations that may be contraindicated.

2.2.7 Acute Perceptual Response to BFR-RE

The addition of BFR to low-load resistance exercise augments the perception of ratings of perceived exertion (RPE) and pain (Freitas et al., 2019; Miller et al., 2020). The extent of RPE and pain experienced during BFR is dependent of the exercise and BFR protocols used (Loenneke et al., 2015; Staunton et al., 2015). In some cases, RPE and pain have been reported to near maximal ratings (Loenneke et al., 2016). The addition of BFR when resistance exercising limits the recovery of fatigue-related metabolites and contractile function within the inter-set rest periods causing development of peripheral fatigue, increasing perception of effort and pain (Husmann et al., 2018). Elevated pain and metabolic accumulation are thought to contribute to a reduced affective response with BFR compared to non-BFR exercise equivalent (Mok et al., 2020). Furthermore, immediately post exercise, mood status assessed via Brunel Mood Scale has shown to be negatively affected by BFR through reduced vigour and increased fatigue following resistance (Silva et al., 2018) and aerobic (Silva et al., 2019) exercise in athletic groups. Nevertheless, evidence suggest that RPE and pain experienced with BFR-RE subsides after a few sessions with an adaptive effect on the perceptual response facilitating an improved tolerance to BFR-RE (Mattocks et al., 2019). The extent that the perceptual response to BFR-RE compares with traditional high load resistance exercise is a contentious area within the BFR literature with some studies reporting lower, similar, and higher perceptual responses with BFR-RE (Freitas et al., 2019; Lixandrão et al., 2019; Loenneke et al., 2015; Miller et al., 2020; Staunton et al., 2015). Though few studies have investigated the perceptual response to BFR-RE, in an older or clinical population.

2.2.8 Hypertrophy Response to BFR-RE

Hypertrophy adaptations have the largest evidence base in the BFR literature. Studies consistently report an increase in myofiber area and muscle cross sectional area following BFR-RE compared with volume-load matched resistance exercise without BFR, which is increased to a similar extent to HL-RE, as measured using histological measures skeletal muscle biopsies, magnetic resonance imaging, computed tomography and ultrasound. (Centner et al., 2019; Grønfeldt et al., 2020). Hypertrophy in both type I and type II fibers are observed, though it is unclear whether there is preferential fibers (Wernbom & Aagaard, 2020). The potential mechanisms for hypertrophy from BFR-RE are derived from mechanical tension and metabolic stress. Both factors mediate mechanism systemic hormone production, increased fast-twitch fibre recruitment, cell swelling and reactive oxygen species which increase protein synthesis and satellite cells and proliferation for inducing hypertrophy (Pearson & Hussain, 2015).

2.2.9 Strength Response to BFR-RE

Both neural adaptations and increases in muscle cross-sectional area contribute to the development of muscular strength (Jones et al., 2008). BFR-RE increases strength compared to matched volume-load resistance exercise without BFR (Centner et al., 2019; Grønfeldt et al., 2020). The extent strength is increased following BFR-RE may depend on the training load used, with higher-loads with BFR resulting in greater improvements in strength (Lixandrão et al., 2018). Typically, BFR-RE result in lower strength increases than high load resistance exercise (Centner et al., 2019; Grønfeldt et al., 2020).

2.2.10 Muscular Endurance Response to BFR-RE

BFR-RE enhances endurance qualities and strength simultaneously (Evans et al., 2010; Fahs et al., 2015). This is also evident when low-load resistance exercise without BFR is performed to failure (Fahs et al., 2015). Given the addition of BFR accelerates the onset of peripheral fatigue, it can be used to facilitate muscular endurance adaptations with lower training intensities, volumes and/or training session durations. BFR-RE has shown to stimulate the upregulation of genes VEGF, VEGFR-2, HIF-1α, PGC-1α and eNOS which are responsible for mitochondrial biogenesis and angiogenesis that enable improved oxidative capacity (Ferguson et al., 2018; Joseph et al., 2006). Furthermore, BFR-RE training has shown to increase resting levels of muscle glycogen and ATP enhancing muscular endurance (Burgomaster et al., 2003).

2.2.11 Vasculature Adaptations to BFR-RE

There is interest in the effect of BFR resistance exercise on vascular function and structure (da Cunha Nascimento et al., 2020; Horiuchi & Okita, 2012; Pereira-Neto et al., 2021). The alteration in normal blood flow caused by BFR application may expose the vasculature to distorted hemodynamic and chemical/metabolic signal that could lead to vascular adaptations. Following 4 weeks of repeated bouts of 5-minute ischemia, forearm blood flow response to acetylcholine increased suggesting improved NO-mediated resistance vessel function in response to a repeated ischemic preconditioning (Kimura et al 2007). Additionally, calf reactive hyperaemic blood flow was shown to improve following 4 weeks of BFR plantar flexion exercise, which was absent in the non-occluded contralateral control (Patterson & Ferguson 2010).

Studies have presented the time course of vascular adaptations following BFR-RE (Hunt et al., 2013; Hunt et al., 2011). Following week 2 of training, popliteal artery flow-mediated dilatation in the BFR-trained leg increased. At week 4, popliteal artery flow-mediated dilatation declined which was accompanied by an increase in dilatory capacity suggesting improvement in NO-independent endothelial function and/or structural remodelling (Naylor et al., 2005). At week 6, flow-mediated dilatation returned to baseline and dilatory capacity plateaued which was accompanied by an increase in maximal diameter of the popliteal artery suggesting a structural enlargement of the conduit vessel, which obviated the need for ongoing functional adaptation.

Hypoxia being the principal stimulus of angiogenesis gives potential for BFR-RE training to stimulate capillary growth (Lundby et al., 2009). BFR-RE has shown to increase transcript (mRNA) expression of VEGF, VEGFR-2, HIF-1α, PGC-1α and eNOS (Ferguson et al., 2018). Repeated exposure to an acute angiogenic response such as this can stimulate capillary growth (Høier et al., 2010; Lundby et al., 2009).

2.2.12 Safety of BFR-RE

The safety of BFR-RE has been carefully considered over the past decade. Reported complications associated with BFR-RE are rarely reported in the literature. There is a consensus that BFR-RE may not pose any greater risk than traditional forms of training (Nakajima et al., 2006; Patterson & Brandner, 2018). However, several concerns about the safety of BFR do exist.

An initial safety concern regarding BFR-RE was the risk of thrombus formation. Research examining BFR-RE with healthy young people and older people with heart disease found no change in blood markers for thrombin generation or intravascular clot formation nor were there reports of any adverse events (Clark et al., 2011; Madarame et al., 2013). Data from a large survey in Japan report BFR-RE sometimes caused the formation of thrombus (Nakajima et al., 2006) though the incidence of deep venous thrombosis (<0.06%) and pulmonary embolism was (<0.01%) is rare. This low incidence rate from thrombus is supported by an international survey of BFR use by practitioners which reported low incidence of superficial thrombophlebitis (0.8%) (Patterson & Brandner, 2018).

Case studies reporting incidences of exertional rhabdomyolysis following BFR-RE have been reported in the literature (Iversen & Rstad, 2010; Tabata et al., 2016). Both cases resulted in hospitalisation with creatine phosphokinase peaks of 55000 $U \cdot L^{-1}$ and 36,000 IU/L. Both cases were discharged after 3 days. One of the cases continued BFR-RE without any further complication. There is no theoretical reason to assume rhabdomyolysis was a result of BFR-RE per se but rather a side effect of rigorous and intense exercise. For example, high-intensity exercise programmes have resulted in rhabdomyolysis (Lozowska et al., 2015; Springer & Clarkson, 2003) with some resulting in CK values of 40,000 IU/L after elbow flexion exercise (Sayers et al., 1999) and exceeding 200,000 IU/L following whole body exercise (Springer & Clarkson, 2003). It is more likely that rigorous physical activity, in general, and unaccustomed activity, can result in exertional rhabdomyolysis. The incidence rate for rhabdomyolysis is extremely rare

(Nakajima et al., 2006; Patterson & Brandner, 2018). However, there is a high likelihood of delayed onset muscle soreness following BFR training (Patterson & Brandner, 2018). Therefore, it is stressed that exercise practitioners use caution with any intervention involving BFR as with any exercise intervention that may cause muscle soreness. To mitigate risk of rhabdomyolysis it is advised participants exercise at a low restrictive pressure (<80% of total arterial occlusive pressure), and at a low exercise intensity (<30% of RM), without performing to failure/exhaustion.

A concern has been raised with the possibility of an exaggerated exercise pressure reflex (EPR), a reflex that contributes to cardiovascular modifications during exercise from the autonomic nervous system, when undertaking BFR-RE (Spranger et al., 2015). It is theorised that reduced blood flow to the working muscles could lead to exercise pressor reflex-mediated cardiovascular complications and excessive blood pressure elevation. Although an abnormal EPR could occur in the apparently healthy, the hesitation is heightened for at-risk populations such as individuals diagnosed with PAD, hypertension or heart failure. These individuals are predisposed to an exaggerated increase in sympathetic nervous system activity during exercise (Cristina-Oliveira et al., 2020; Spranger et al., 2015). An awareness of this potential complication is justified. However, it is likely the risk of an adverse event can be lessened by using cuff inflation pressures relative to the participant (for example 50% AOP) and by reducing the overall BFR pressure (Jessee et al., 2016). However, to the authors knowledge no cardiovascular complications have occurred following BF-RE. Furthermore, a review of the haemodynamic response to BFR-RE show an

increased blood pressure response with the addition of BFR to resistance exercise, these are consistently within the normal range excepted with exercise and do appear to increase over and above high load resistance exercise (Neto et al., 2017).

It is critical to ensure the risks of BFR-RE are identified, controlled and minimised to maximise patient safety. Exercise that is perceptually least stressful for the patient will be identified to ensure safety and encourage exercise compliance. The issues associated with BFR-RE can be mitigated by utilising the lowest restrictive cuff pressure and resistance load that provides a training stimulus. It is proposed to use a relative restrictive cuff pressure of 50% AOP and an resistance load of 20% 1RM. To the researcher's knowledge this is the lowest effective restrictive cuff pressure and resistance load reported in the literature applied to older adults (Vechin et al., 2015). It is important to note that the adaptations associated with BFR-RE are thought to occur when venous clearance of metabolites is reduced not when arterial blood flow is restricted; though a change in arterial blood flow is expected as a consequence of external leg pressure. Restrictive cuff pressures of 50% AOP minimises disruption of arterial blood flow and subsequent vasoconstriction of the artery of the BFR limb. In contrast, a restrictive cuff pressure of 80% arterial occlusion pressure reduces arterial diameter, blood flow and blood velocity when cuff is inflated (Hunt et al., 2016). Furthermore, lower BFR pressures and resistance loads are associated with lower RPE and pain during exercise (Loenneke et al., 2015). This has important implications regarding the tolerability and safety of BFR-RE.

2.2.13 Clinical Applications of BFR-RE

There is a strong growing interest of the clinical utility of BFR-RE (Patterson et al., 2017; Vanwye et al., 2017). However, the extent BFR-RE is applied to varying clinical populations is minimal. Strong evidence exists of BFR-RE efficacy in older adults and patients with knee osteoarthritis (Hughes et al., 2017). Some evidence suggest BFR-RE is safe and possibly efficacious in polymyositis and dermatomyositis (Jørgensen et al., 2016; Mattar et al., 2014). Other studies have investigated the acute responses to BFR exercise to infer its safety (Pinto et al., 2018) report the haemodynamic response low load resistance exercise is elevated with the addition of BFR, but this is comparable to high-load resistance exercise in hypertensive patients. Madarame et al., (2013) applied BFR-RE to stable ischaemic heart disease reporting the addition BFR to low load resistance exercise did not affect exercise-induced haemostatic and inflammatory response. There is evidence to suggest of the clinical utility of BFR-RE in the field (Patterson & Brandner, 2018) therefore formal investigations are crucial to elucidate the full extent of the safety and effectiveness of BFR-RE in different clinical populations.

2.2.14 Rationale for BFR-RE in IC

BFR is a tool which can enhance the training stimulus if applied while performing low-load resistance exercise. This is achieved by the restrictive cuff limiting the venous clearance of muscle metabolites during exercise, thereby accelerating the metabolic demand on the muscle and subsequent development of peripheral fatigue to condition the muscle. The stimulus is sufficient to induce hypertrophy of type I and type II muscle fibers, angiogenesis, mitochondrial protein synthesis and muscle strength, and improve arterial function before arterial structural

enlargement in healthy adults. Such adaptations occurring from BFR-RE are comparable to resistance exercise when performed at low load to muscular failure or at high load.

Low-load resistance exercise to failure may not be appropriate for patients with IC. Such protocols are associated with high levels of exercise volume, and maximal RPE and pain and as such are difficult to maintain through an exercise programme. High load resistance exercise may be inappropriate for many patients with IC who may struggle with the high mechanical load, and the increased risk of musculoskeletal injury.

If patients with IC respond to BFR-RE similarly to healthy adults, an increase in type I and type II size, with increase capillary number and density and improved mitochondrial function and increased muscle mass and strength would address the skeletal muscle dysfunction and reduced microvascular flow associated with IC that contribute to an impaired exercise performance. However, it is not known if BFR-RE is safe or tolerable for patients with IC, therefore such investigations must be made.

2.2.15 Feasibility Trials in Medical Research

The Medical Research Council (MRC) provide guidance for developing and evaluating complex interventions. The MRC recommends a carefully phased and systematic approach to interventions that begins by identifying relevant evidence and theory, then conducting feasibility or pilot trials where procedures and protocols can be tested (**FIGURE 8**) (Skivington et al., 2021). Modelling an

intervention before a full-scale evaluation can identify weaknesses, lead to refinement, and indicate whether a full-scale trial is warranted (Skivington et al., 2021).

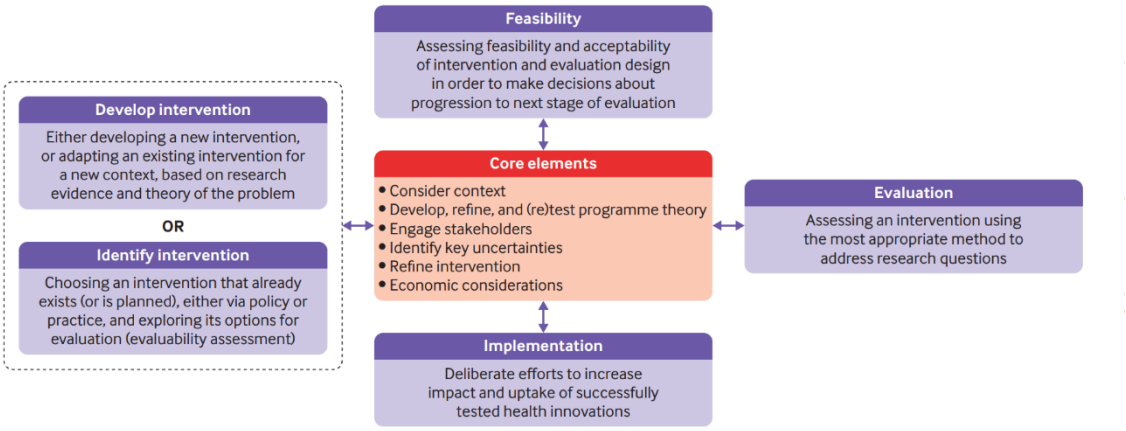


FIGURE 8: Medical Research Council framework for complex interventions (Skivington et al., 2021).

The feasibility is designed to assess predefined progression criteria that relate to the evaluation design. The purpose of the feasibility trial is to provide estimates of recruitment and retention and acceptability of procedures and protocols. The feasibility trial should reduce uncertainty around recruitment, data collection, retention, outcomes and analysis and the proposed intervention and develop design offering optimal content and delivery, acceptability, adherence and delivery of intervention (Skivington et al., 2021). Therefore, the evaluation of feasibility studies provides a valuable insight into whether an intervention is plausible or effective and how it can be optimised. The value of feasibility testing is now widely accepted (Eldridge et al., 2016; Thabane & Lancaster, 2019).

3 General Methods

3.1 Overview of Studies

The first Experimental Chapter (Chapter Four) examined the acute responses of BFR-RE in comparison to conventional resistance exercise in healthy young and older adults with a view of exploring the tolerability of the BFR-RE protocol which would be used for patients with PAD. Fifteen young and twenty older adults performed two lower body resistance exercises in a single session at low-load with BFR (LL-BFR), low-load without BFR (LL) and moderate-load without BFR (ML). Perceptual responses RPE, pain, feeling scale, and cardiovascular responses HR and blood pressure indicated participants tolerance to the exercise protocols and linear mixed models were used to compare between exercise groups.

The second Experimental Chapter (Chapter Five) analysed the test-retest reliability of ABPI, ultrasound measurement of vastus lateralis muscle thickness, unilateral isometric knee extension maximal voluntary torque and 6-minute walk test (6MWT) in patients with IC to understand the variability of measures within patients with IC and determine the smallest worthwhile change.

The third Experimental Chapter (Chapter Six) explored the safety, feasibility and preliminary efficacy of an 8-week lower-body resistance exercise with BFR programme with 30 IC patients.

3.2 Recruitment

Chapter Four recruitment and ethics

Fifteen young (20 – 29 years of age, all males) and 20 older (60 – 74 years of age, males *n* = 10 and females *n* = 10) adults volunteered to take part in Study 1 recruited via convenience sampling from Sheffield Hallam University and Graves Health Centre (Sheffield, UK), respectively.

Participants were provided with verbal and written information regarding the study's tasks with associated risks before to participating in the study (Appendix 1). Following this, participants were screened for any contraindications to participation. All participants had no known history of peripheral, neurological, cardiovascular, pulmonary, or metabolic disorders, musculoskeletal injuries, or self-reported tobacco users. All participants were physically active but was not involved in resistance exercise for the previous 6 months prior to participating.

The study was approved by the Ethics Committee of Sheffield Hallam University (project identification: ER10932988), and written informed consent was obtained from each participant prior to taking part in study (Appendix 1). The study was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Chapter Five and Six recruitment and ethics

Clinically diagnosed patients with stable IC (determined by a physician) were recruited from clinics from the Sheffield Vascular Institute, at the Northern General Hospital, Sheffield, UK and Assessment and Rehabilitation Centre,

Sheffield, UK. Selection was based on the patient's physical examination confirming IC by Consultant or the Vascular Nurse Specialists and on the inclusion and exclusion criteria described below (**TABLE 7**). Patients who were interested in taking part in the study were given an invitation letter and participant information sheet (Appendix 1). Patients who respond to the invitation letter were contacted by the research team (TP). During this contact patients were screened by the collaborating physician (SN) to ensure suitability to participate and were given the opportunity to ask questions. Patients satisfying the study criteria were invited to The Centre for Sport and Exercise Science to fully enrol into the study. Potential recruits who declined to participate or do not respond to the invitation letter were not contacted further.

TABLE 7: Eligibility criteria for patients with IC to volunteer to participate.

Inclusion Criteria
• Men and women >18 years of age. • Clinical symptoms and signs of lower-limb PAD supported by the presence of usual risk factors. • Symptoms of stable intermittent claudication of >6 months. • A resting ABPI <0.9. • A decrease in ABPI of >0.15 after maximum walking exercise if resting ABPI was >0.9. • Ability to undertake exercise testing and training.
Exclusion Criteria
• Symptoms of stable intermittent claudication of <6 months. • A resting ABPI >0.9. • Inability to obtain an ABPI measurement due to non-compressible vessels. • Significant change in walking ability within the last 12 months (denoting unstable claudication). • Exhibiting features of critical limb ischaemia. • Abnormal resting electrocardiogram readings. • A revascularisation procedure or other major surgery within the previous 12 months. • Major surgery or myocardial infarction within the previous 12 months. • Major surgery scheduled during the intervention period. • Previous stroke. • Previous thrombosis.

The research was approved by the Health Research Authority Yorkshire and The Humber – Leeds West Research Ethics Committee (IRAS: 260419) (Appendix 2). Written informed consent was obtained from each patient prior to investigation which was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

3.3 Exercise Protocol

Lower-Body Resistance Exercises

Two lower-body resistance exercises were utilised in this thesis, performed bilaterally and dynamically with concentric-eccentric muscle actions (a concentric 'lifting' phase followed by the eccentric 'lowering' phase).

First lower-body resistance exercise was the horizontal leg press. The leg press is performed using closed-chain kinetic effort and the hip and knee extension involves large lower-body muscle groups (quadriceps, hamstring, gluteus and gastrocnemius) (Silva et al., 2008; Ivey et al., 2017). The specific training of these muscle groups is closely related to jumping, running, and athletic performance in general (Escamilla et al., 2001), and consequently the leg press exercise is widely used for strengthening the lower body (Centner et al., 2018). Participants performed the leg press in a seated position with the lower back in contact with the seat, feet placed on the platform at shoulder-width apart, knees flexed at 90°, and hands placed on the side handles. With instruction, participants performed a purely concentric action requiring simultaneous extension of hip and knee, then slowly returned to the initial position before performing the next repetition.

Second lower-body resistance exercise was knee extension. The knee extension is performed using open-chain kinetic effort involving quadriceps. The knee extensors in particular appear to be crucial in a variety of functional tasks, such as walking, chair rising and stair climbing (Ploutz-Snyder et al., 2002). Participants performed the knee extension in a seated position with the back supported in contact with the seat, knees at 90° flexion and hands placed on the

side handles. With instruction, participants performed a purely concentric action requiring extension of the knee, then slowly returned to the initial position before performing the next repetition.

Blood Flow Restriction

Pneumatic 13 x 85 cm nylon pressure cuffs (SC12, Hokanson, Indianapolis, USA) controlled by a Rapid Cuff Inflator and a Cuff Inflator Air Source (E20 Rapid cuff inflator and AG101 Cuff Inflator Air Source, Hokanson, Indianapolis, USA) were used to implement venous occlusion of the lower body during BFR-RE. A relative BFR stimulus was determined by a restrictive pressure based on 50% AOP measured at rest (McEwen et al., 2019; Patterson et al., 2017).

The purpose of using relative restrictive cuff pressures was to attempt to minimise the variability of limb blood flow that is restricted between individuals compared to using arbitrary restrictive cuff pressures or a restrictive cuff pressure based on a percentage of systolic blood pressure of the arm, which are both more influenced by individual participant differences in body composition and hemodynamics (Loenneke et al., 2012; McEwen et al., 2019; Patterson et al., 2017, 2019). The relative restrictive cuff pressure used within this thesis (50% AOP) was chosen to balance participant comfort with an established restrictive cuff pressure producing favourable adaptations from BFR-RE (Counts et al., 2016; Fatela et al., 2016; Loenneke et al., 2015; Soligon et al., 2018).

AOP was measured in accordance with established methods (Laurentino et al., 2020). Patients laid in a recumbent position in a quiet unlit room for 10 min. A 13

x 85 cm nylon cuff (SC12, Hokanson, Indianapolis, USA) was applied at the most proximal portion of the thigh and 8 MHz vascular Doppler probe (HI-Dop vascular Doppler, Ana Wiz, Surrey, UK) positioned on the posterior portion of the medial malleolus on the branches of the tibial artery of the same leg. The cuff was inflated (E20 Rapid cuff inflator and AG101 Cuff Inflator Air Source, Hokanson, Indianapolis, USA) until interruption of auditory signal of arterial blood flow suggesting arterial occlusion and the final pressure was recorded. The procedure was repeated for the opposite leg. The mean AOP of both legs was used to determine the restrictive cuff pressure applied during BFR-RE.

It is important to consider postural changes and its effect on hydrostatic pressure when measuring AOP. For example, AOP in a seated position has shown to be 8 – 16% higher than in a supine position (Hughes et al., 2018; Sieljacks et al., 2018). Therefore, it is essential that the postural position during AOP measurement mimics the postural position during BFR-RE to minimise an over/underestimation of the cuff pressure. During AOP measurement in this research, participants were positioned in a recumbent position with a hip angle that was like the position on the leg press and knee extension machines. AOP has shown to be highly reproducible in both seated (ICC = 0.975; 95% CI [0.932–0.994], CV = 1.82%, 95% CI [0.95–2.69]) and supine (ICC = 0.982; 95% CI [0.932–0.995], CV = 2.94%; 95% CI [1.90–3.98]) positions (Hughes et al., 2018).

3.4 Assessments

Ankle-Brachial Pressure Index

The ABPI is a non-invasive test for the screening, diagnosis, and haemodynamic monitoring of PAD (Gerhard-Herman et al., 2017). A low ABPI (<0.90) defines the presence of PAD with lower ABPI indicating greater hemodynamically significant PAD (Aboyans et al., 2012). While an improvement in ABPI is unlikely following exercise (Harwood et al., 2016) it is important to assess ABPI in case of worsening. A change in ABPI of 0.15 is clinically significant (Jeelani et al., 2000). If a negative change of 0.15 occurs, it could signify a detrimental effect of BFR-RE in PAD.

Whilst in a recumbent position with the lower-limb area exposed, the systolic pressures in the posterior tibial and dorsalis pedis arteries were determined in both feet using a handheld vascular Doppler device (HI-Dop vascular Doppler, Ana Wiz, Surrey, UK) and manual sphygmomanometer. The systolic pressure in the brachial artery of each arm was also recorded. The ABPI for each leg was calculated by dividing the mean values from the dorsalis pedis and posterior tibial arteries by the mean values from the brachial artery in each arm. The higher of the two brachial pressures was used if the two brachial pressures differed by more than 10 mmHg, in which case subclavian stenosis was suspected (Aboyans et al., 2012).

Six-Minute Walk Test

The American Thoracic Society guidelines provide instructions of how to conduct the 6MWT reliably (Enright, 2003). It is important to ensure the 6MWT is

performed in a long, flat, and straight corridor on hard flooring with the walking circuit set at a minimum of 20 m in length. Patients are required to complete as many circuits as possible in 6-minutes. Patients are allowed to set their own pace and stop if required. It is critical not to walk with patients when conducting the test. Standardised phrases of verbal encouragement were used as encouragement and enthusiasm can influence performance by 30% (Enright, 2003).

The 6MWT is a well-validated measure of walking performance that is reliable in PAD (R = 0.94; CV = 10.4%) (Montgomery & Gardner, 1998) and is simple to conduct (McDermott et al., 2011). Among patients with IC, the 6MWT is sensitive to change in response to interventions (Mcdermott et al., 2009; Nordanstig et al., 2014), predicts mobility loss and mortality (McDermott et al., 2011), is closely correlated with physical activity levels in the community (McDermott et al., 2008) and is not associated with learning effects with repeated testing (Sandberg et al., 2019). Additionally, the minimal clinically important difference in 6MWT distance, which represents the smallest threshold change in an outcome measure that is perceived beneficial to the patient has been reported in patients with IC (Gardner et al., 2018). After 3 months of exercise intervention, small (5%), moderate (25%), and large (40%) clinically important changes in the 6MWT distance were found to be at 12 m, 32 m, and 34 m, respectively (Gardner et al., 2018).

Many randomised controlled trials have used treadmill walking assessments as the primary outcomes following therapeutic interventions in patients with IC (Lane et al., 2014). While employing treadmill walking assessments would allow

comparisons between studies there are significant limitations to treadmill walking as an outcome which have been presented previously (Mcdermott et al., 2014). It is argued that a motorised treadmill assessments requires balance and the ability to maintain constant rhythmic gait to match the speed of the treadmill which can be difficult for the patient. As a result, patients frequently touch or hold onto the handrail support to maintain balance therefore does not reflect normal walking (Mcdermott et al., 2014). Additionally, treadmills with handrail supports are associated with a significant learning effect and longer maximal walking distances (Gardner et al., 1991). Lastly, a meaningful change in treadmill walking performance has not been defined.

Vastus Lateralis Muscle Thickness

Ultrasound Imaging was used to quantify changes in muscle size in this thesis. Vastus Lateralis muscle thickness (VL-MT) was assessed from images obtained at rest using B-mode ultrasonography (L14-4, Sonimage MX1, Konica Minolta, Tokyo, Japan) and image analysis software (ImageJ, U.S. National Institutes of Health, Maryland, USA) by the same researcher (TP). Standardised procedures were followed (Ticinesi et al., 2018). This requires participants to be resting for 15 minutes in a supine position to allow fluid shifts to occur and maintain a resting condition throughout the test. The reference point for ultrasound imaging was the midpoint between the greater trochanter and lateral epicondyle and the midpoint between the medial and lateral edges of the vastus lateralis provided. The transducer was placed longitudinally to the thigh along the mid-sagittal axis of the Vastus Lateralis, and carefully aligned to the fascicle plane to clearly visualise fascicles on the ultrasound screen. Generous amounts of surface gel is

recommended and as the little pressure as possible when placing the probe on the skin to promote acoustic coupling while avoiding dermal deforming. To measure VL-MT clear image of the superficial and deep aponeurosis were obtained and recorded (**FIGURE 9**). VL-MT was determined as the mean distance between the superficial aponeurosis and the deep aponeurosis at three different positions (left, middle, right) of the picture. The mean of the three measures was calculated for and used for analysis.

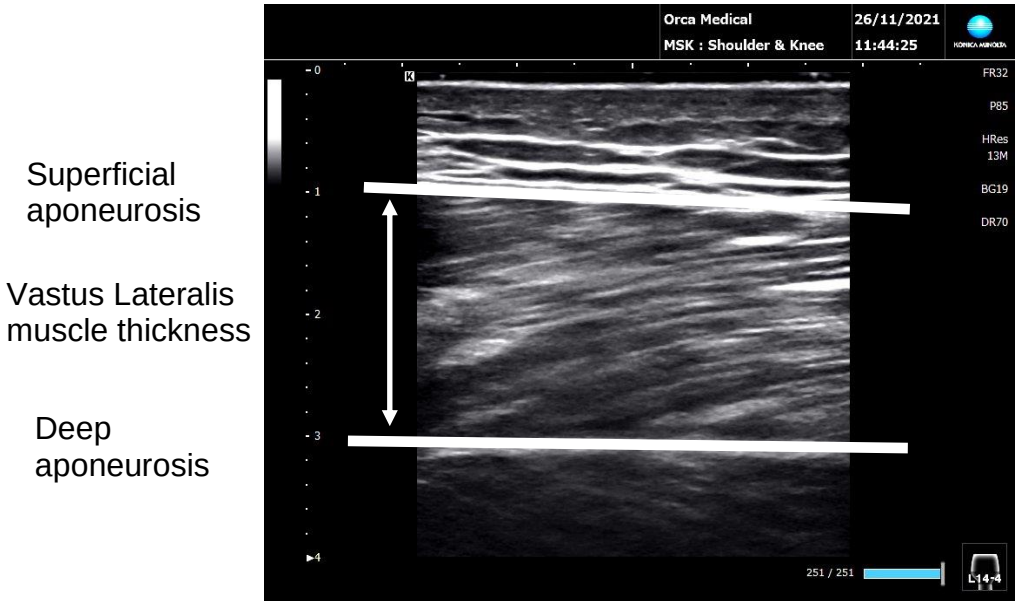


Figure 9: Representative recording of vastus lateralis muscle thickness.

Many randomised controlled trials have measured calf muscle size as the outcome following walking exercise interventions in patients with IC (Garg et al., 2011; McDermott et al., 2012; Mcdermott et al., 2020). The purpose of measuring VL-MT in this thesis was to see if BFR-RE induces hypertrophy in IC patients. The quadricep is the main muscle group used during leg press and knee extension resistance exercises therefore is more likely to observe changes in muscle size.

Several studies have reported the measurement of muscle thickness in different scenarios to assess muscle hypertrophy (Bjørnsen et al., 2016; Franchi et al., 2015; Hernandez et al., 2015; Narici et al., 2011; Reeves et al., 2009). VL-MT is easily determined with ultrasound imaging and has shown highly correlated to cross-sectional area of muscle (Abe et al., 1997). B-mode ultrasound imaging of VL-MT has shown to be a highly reproducible (0.96 – 0.99 ICC) with appropriate operator training (Franchi et al., 2018; Reeves et al., 2004).

Maximal Voluntary Torque

Unilateral isometric knee extension maximal voluntary torque (MVT) was measured is this thesis using the Cybex Humac Norm Isokinetic Extremity System (Computer Sports Medicine Incorporated, Massachusetts, USA) to indicate changes in lower-body strength. Isokinetic dynamometry is the gold standard for measuring muscle function (Drouin et al., 2004). An isokinetic dynamometer can operate in an isometric mode to measure maximal voluntary torque (MVT) in a predetermined position without limb movement allowing a safe maximal effort to be performed (Alvares et al., 2015). Isometric MVT are a well-

established technique to assess lower-extremity strength in PAD (Mcdermott et al., 2009; Mcdermott et al., 2004; Scott-Okafor et al., 2001)**.** Isometric knee extension MVT is associated independently with lower extremity functioning and physical activity level in PAD (Ferrucci et al., 1997; Mcdermott et al., 2004)**.** Isometric MVT has previously shown excellent reliability (Drouin et al., 2004; van Driessche et al., 2018),

Patients were seated with the knee and hip joints at 90° flexion, with the waist and thigh strapped to limit extraneous movements. Patients first performed a warm-up consisting of 5 repetitions of 3 second submaximal isometric knee extensions. Following this, patients were asked to perform three MVT lasting 3 seconds with minimum 60 seconds rest between each effort. During the determination of MVT, patients received visual feedback of the force signal and strong verbal encouragement to motivate maximal efforts. The highest peak force of the three MVT efforts were used for analysis.

3.5 Statistical Approaches

The statistical and data approaches for each experimental chapter and the rationale for each is presented within the individual experimental chapters as appropriate.

4 Comparative Perceptual, Affective and Physiological Responses Between Resistance Exercise with and without Blood Flow Restriction in Young and Older Adults

4.1 Abstract

Purpose: This study explored exercise tolerability parameters during different lower-body resistances exercises when performed at low-load with Blood Flow Restriction (LL-BFR), low-load (LL) and moderate-load (ML) in healthy young and older adults.

Methods: Fifteen young men (24.0 ± 3.3 years) and 20 older men and women (64.3 ± 4.2 years) were recruited. Participants completed the following exercise sessions on separate occasions in a randomised design: (1) LL-BFR, (2) LL, and (3) ML. Each exercise session involved 4 sets of leg press and knee extension. Ratings of perceived exertion, pain, delayed onset muscle soreness, Physical Activity Affect Scale (PAAS), heart rate (HR) and blood pressure were measured.

Results: Ratings of pain were highest during LL-BFR than LL (4.1 ± 1.5 CR-10$^+$ vs 2.5 ± 1.1 CR-10$^+$, $p < 0.001$; $d = 1.4 – 1.5$) and ML (4.1 ± 1.5 CR-10$^+$ vs 2.9 ± 1.1 CR-10$^+$, $p \leq 0.002$; $d = 0.9 – 1.0$). PAAS subscales positive affect, negative affect, fatigue, and tranquillity following LL-BFR were comparable to LL and ML. HR_{mean} ($\Delta = 8\%$; $p \leq 0.014$; $d = 0.7 – 1.3$), HR_{peak} ($\Delta = 8\%$; $p \leq 0.002$; $d = 0.7 – 0.9$) and rate pressure product ($\Delta = 12\%$; $p \leq 0.002$; $d = 0.9$) were increased with LL-BFR compared to LL. In all exercise sessions RPE (12.5 ± 1.2 CR-20 vs 10.8 ± 1.2 CR-20; $p < 0.001$; $d = 1.4$) and pain (3.8 ± 1.5 CR-10$^+$ vs 2.5 ± 1.3 CR-10$^+$; $p < 0.001$; $d = 1.3 – 1.7$) were higher during knee extension compared to leg press, which may be further elevated by LL-BFR.

Conclusion: LL-BFR is less tolerable than resistance exercise without BFR through elevated pain. Furthermore, the type of lower body resistance exercise can have a substantial effect on the perceptual response.

4.2 Introduction

Developing muscle mass and strength in clinical populations in rehabilitation or with certain chronic conditions is pivotal for recovery and management (Beaudart et al., 2016; Lane et al., 2017; McAlindon et al., 2014). Resistance exercise performed with moderate- to high-loads (≥60% of one repetition maximum; 1RM) are typically required for hypertrophy and strength adaptations (Garber et al., 2011). Though such loads may be unattainable or contraindicated due to underlying musculoskeletal disorder and/or muscle weakness. BFR-RE has received substantial attention in scientific literature during the last decade as a prospective alternative modality to promote beneficial muscular adaptations in healthy, clinical, and athletic populations (Centner et al., 2018; Grønfeldt et al., 2020; Hughes et al., 2017; Loenneke, Wilson, et al., 2012; Scott et al., 2016; Slysz et al., 2016). The technique utilises pneumatic cuffs or elastic wraps to apply an external pressure around the proximal region of the exercising limb to partially restrict arterial blood flow and occlude venous return whilst lifting low loads (20 - 40% 1RM; 15 – 30 repetitions per set) (Patterson et al., 2019a). Consequently, intramuscular oxygen delivery and venous clearance of metabolites are impaired which elevates levels of metabolic stress during sustained mechanical tension (Pearson & Hussain, 2015). This activates systemic hormone production (Manini et al., 2012), myofibrillar and mitochondrial protein synthesis (Groennebaek et al., 2018; Sieljacks, Wang, et al., 2019), and

angiogenesis (Larkin et al., 2012). As a result, muscle size**,** maximal strength, and local muscular endurance are enhanced following BFR resistance exercise training (Fahs et al., 2015; Kacin & Strazar, 2011; Laurentino et al., 2012)**.**

Although the benefit of BFR-RE to elicit long-term muscular adaptations with minimal mechanical stress on the musculoskeletal system through using low loads could prove valuable to clinical populations, tolerability of the technique is of concern to practitioners (Patterson & Brandner, 2018). The addition of BFR to exercise is associated with an increased RPE and pain, HR, MAP, and RPP (Loenneke et al., 2015; Scott et al., 2018; Staunton et al., 2015; Vieira et al., 2013), sensations such as dizziness, numbness, muscle burning and aching (Brandner et al., 2018; Patterson & Brandner, 2018; Weatherholt et al., 2013), and a reduced affective valence response and decrements of mood states (Mok et al., 2020; Silva et al., 2018, 2019). Such perceptual, affective, and physiological responses to exercise could deter exercise participation (Ekkekakis et al., 2011; Fisher et al., 2017; Kim et al., 2017).

To what extent these responses differ to resistance exercise without BFR remains a contentious area within the BFR literature. Studies have reported lower, similar and higher perceptual and physiological responses to BFR-RE in comparison to high-load resistance exercise without BFR, with inconsistencies in reports likely due to varying exercise protocols and BFR methods used (Dankel et al., 2019; Freitas et al., 2019; Lixandrão et al., 2019; Loenneke et al., 2015; Manini et al., 2012; Mattocks et al., 2019; Pinto et al., 2018; Poton & Polito, 2014; Scott et al., 2018). Furthermore, studies including affective responses and pain specific to

older adults are lacking, and investigations are required given BFR-RE is recommended for this population (Centner et al., 2018; Hughes et al., 2017). Additionally, BFR methodology is critical to the tolerability of the technique. Restrictive cuff pressures (Singer et al., 2020; Soligon et al., 2018), cuff width (Rossow et al., 2012; Spitz et al., 2021), type of cuff (Miller et al., 2020) and exercise load (Loenneke et al., 2015) can have marked implications onto the perceptual or physiological response. However, only one study has considered exercise selection, and this studied older women (Scott et al., 2018)**.** Lower body resistance exercises leg press and knee extension are most prescribed with BFR (Patterson & Brandner, 2018). Examining the perceptual and physiological differences between the exercises in both young and older adults and determining exercise that is perceived favourably is useful for practitioners using BFR-RE to develop exercise programmes that encourage exercise adherence and frequency.

If the wider application of BFR-RE is to be utilised with clinical populations, it is important to first investigate parameters of tolerability in young and older adults without musculoskeletal disorders or muscle weakness. It is key to compare resistance exercise with and without BFR during different exercises to make ecologically valid conclusions that will improve our understanding of the tolerability of the technique and inform practice. This study explores the acute effects of low-load resistance exercise with BFR on perceptual, affective, and physiological responses in comparison to low-load and moderate-load resistance exercise without BFR in young and older adults.

4.3 Methods

Participants

This study was approved by the Ethics Committee of Sheffield Hallam University (ER10932988). All participants were required to meet the following inclusion criteria; 1) did not engage in resistance exercise in the previous six months; 2) did not self-report uncontrolled hypertension (>150/90 mmHg), musculoskeletal, neurological, or vascular disease/injury; 3) non-smokers, defined as not used tobacco and related products in the previous 6 months; and 4) did not meet more than one risk factor for thromboembolism, which includes the following; obesity (BMI > 30 kg/m^2); diagnosed with Crohn's disease; a past fracture of hip, pelvis, or femur; major surgery within the last 6 months; varicose veins; a family or personal history of deep vein thrombosis or pulmonary embolism (Motykie et al., 2000). Fifteen young adults (15 men, age 24.0 ± 3.3 years, stature 179.2 ± 5.2 cm, body mass 84.8 ± 13.8 kg, BMI 26.4 ± 3.8 kg/m^{-2}) and twenty older adults (10 men and 10 women, age 64.3 ± 4.2 years, stature 171.3 ± 9.8 cm, body mass 75.1 ± 11.5 kg, BMI 25.6 ± 3.7 kg/m^{-2}) volunteered to take part in the study. The study was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). All participants were informed of the experimental procedures and risks that were associated with the study before giving written informed consent. Participants underwent familiarisation sessions in which they were orientated to the exercise equipment, the exercise protocols, measures, and study procedures prior to the experimental trials.

Study Design

Participants attended the laboratory for two preliminary visits before the main resistance exercise sessions. During the first visit, anthropometric data (stature

and body mass) and resting physiological data (SBP, DBP and arterial occlusion pressure) were collected. Participants were then familiarised with exercising on the horizontal leg press machine (Pro 2 Seated Leg Press, Life-fitness, Illinois, USA) and knee extension machine (SP100, TECA Fitness, Montesilvano, Italy), and perceptual (RPE and Pain) and affective (Physical Activity Affect Scale, PAAS) measures. During the second visit, participants completed 1RM testing for both leg press and knee extension using the 10RM approach. This was adopted as it was anticipated the participant's true 1RM would exceed the load capacity of the resistance exercise machines, participants may have felt uncomfortable performing their true 1RM which may impact on participation and to minimise risk of musculoskeletal injury. Participants were then familiarised with the three experimental conditions, which consisted of completing the first two sets of each resistance exercise protocol.

A randomised crossover design was utilised to compare the perceptual, affective, and physiological responses to lower-body resistance exercise when performed at (1) low-load with BFR (LL-BFR), (2) low-load (LL), and (3) moderate-load (ML). Participants visited the laboratory on three occasions at the same time of day which were separated by a minimum of 5 days to remove the effects of the previous visit. Participants were instructed to avoid vigorous exercise 48 h, alcohol 24 h and caffeine 8 h prior each visit. Each resistance exercise session consisted of leg press and knee extension. To minimise trial order effects for comparisons made between condition and exercise, the order the exercises were performed was randomised.

Determination of Arterial Occlusion Pressure

AOP was measured for both legs and the mean pressure of both legs was used to determine the restrictive cuff pressure applied during LL-BFR in accordance with established methods (Laurentino et al., 2020). Participants laid in a recumbent position in a quiet unlit room for 10 min. A 13 x 85 cm nylon cuff (SC12, Hokanson, Indianapolis, USA) was applied at the most proximal portion of the thigh and 8 MHz vascular Doppler probe (HI-Dop vascular Doppler, Ana Wiz, Surrey, UK) positioned on the posterior portion of the medial malleolus on the branches of the tibial artery of the same leg. The cuff was inflated (E20 Rapid cuff inflator and AG101 Cuff Inflator Air Source, Hokanson, Indianapolis, USA) until interruption of auditory signal of arterial blood flow suggesting arterial occlusion and the final pressure was recorded. This was then repeated for the opposite leg. The mean AOP for young adults and older adults was 161.5 ± 32.0 mmHg and 188.3 ± 24.8 mmHg, respectively.

Predicted One Repetition Maximum

1RM for leg press and knee extension was estimated using repetitions to failure method based on previously tested protocols (Cook et al., 2017; Kilgas et al., 2019) to determine the load used for each condition. Following a standardised warm-up by performing 5 min of light cycling (RPE of 11 CR-20), participants performed 10 repetitions at a load of low effort. The load was progressively increased until momentary failure occurred within 10 repetitions. Momentary failure was determined when, despite maximum effort, the participant was unable to complete a repetition through the full range of motion. 1RM was then predicted using the Brzycki equation (Brzycki, 1993): load ÷ (1.0278- [0.0278 × number of

repetitions]). The Brzycki equation has shown excellent predictive accuracy of actual 1RM for leg press (0.96 ICC) and knee extension (0.99 ICC) (McNair et al., 2011). The predicted 1RM for leg press and knee extension was 234.7 ± 31.3 kg and 127.2 ± 15.8 kg for young adults, and 190.0 ± 68.6 kg and 64.0 ± 23.7 kg for older adults.

Resistance Exercise Protocols

Resistance exercise sessions began with a standardised warm-up by performing 5 min of cycling, with the intensity progressively ramped to an RPE of 12 CR-20. Participants then completed programmed protocols for seated 45° horizontal leg press and knee extension. Exercises were separated by a 5 min passive rest period. Exercises were performed bilaterally with repetitions executed every 3 s (1.5 s during concentric phase and 1.5 s during eccentric phase) with support from a metronome. For young adults, LL-BFR and LL protocols involved 1 set of 30 repetitions followed by 3 sets of 15 repetitions with 30 s recovery periods between sets at a load of 20% 1RM for both leg press and knee extension. Older adults were programmed similar protocols for LL-BFR and LL, though knee extension involved 4 sets of 15 repetitions. During LL-BFR, a 13 cm wide nylon pneumatic cuff (SC12L segmental pressure Cuff, Hokanson, Indianapolis, USA) was placed around the proximal region of the legs. The cuff was inflated (E20 Rapid Cuff Inflator and AG101 Cuff Inflator Air Source, Hokanson, Indianapolis, USA) to 50% of arterial occlusion pressure 15 s before starting either exercise, the pressure was maintained during the exercise bout and was then deflated after the last repetition once RPE, pain, HR and blood pressure was measured. To note, the cuff was deflated during the 5 min rest period between exercises. The

ML-RE protocol involved 4 sets of 10 repetitions with 60 s recovery periods between sets at a load of 60% 1RM for leg press and knee extension for both young adults and older adults.

Perceptual Responses

RPE was measured using the CR-20 scale (Borg, 1998) and pain using the CR-10^{+} modified pain scale (Borg, 1998) immediately (within 5 s) following each set of exercise. The mean RPE and pain across all sets were used for analysis. Both CR-20 and CR-10^{+} scales have been shown to be valid and reliable in exercise and pain studies (Borg, 1982, 1998) and have been used to quantify RPE and pain in previous BFR related studies (Freitas et al., 2019; Loenneke et al., 2015). Delayed onset muscle soreness (DOMS) of the lower body was obtained 24 h and 48 h following each resistance exercise session after requesting rating via text message using the CR-10^{+} modified pain scale (Borg, 1982). To gauge soreness of the lower body, participants were asked to flex and extend both knees and press into the muscle with their hands before providing their ratings.

Affective Responses

The PAAS (Lox et al., 2000) was used to assess the affective response to resistance exercise session and was measured upon the arrival of the laboratory at rest and immediately (within 60 s) post exercise. The PAAS questionnaire includes 12 feelings which are equally divided into 4 subscales: positive affect ('enthusiastic', 'energetic' and 'upbeat'), negative affect ('miserable', 'discouraged' and 'crummy'), tranquillity ('calm', 'relaxed' and 'peaceful') and fatigue ('fatigued', 'tired' and 'worn-out'). Participants were asked to rate their current affective state

for each item on a scale; do not feel (0), feel slightly (1), feel moderately (2), feel strongly (3) or feel very strongly (4). A mean score for each subscale was calculated and used for analysis. The PAAS is sensitive to affective changes during exercise (Kwan & Bryan, 2010), and shown convergent and discriminant validity in both active and sedentary individuals (Carpenter et al., 2010).

Physiological Responses

Blood pressure was assessed using an automatic monitor (HEM-8712, Omron, Healthcare, Kyoto, Japan) at rest and immediately following each exercise according to standardised operating procedures. HR was monitored using a traditional chest strap (TICKR, Wahoo, Atlanta, USA) throughout the resistance exercise session and recorded every 5 s excluding rest periods. These data were used to calculate HR_{mean}, HR_{peak}, MAP (calculated as 1/3 (SBP-DBP) + DBP), PP (calculated as SBP – DBP) and RPP (calculated as SBP x HR/100).

Statistical Analysis

Data for young adults and older adults were analysed separately but followed the same analysis procedures. Data are presented as means ± SD unless indicated otherwise. Prior to analysis the Shapiro-Wilk test confirmed that perceptual and physiological data were normally distributed, and affective data were not normally distributed. Dependent variables during exercise (RPE, pain and physiological parameters) were compared between conditions (LL-BFR, LL, and ML) and exercise (leg press and knee extension) using linear mixed models. Condition and exercise were set as fixed factors and participants were set as random factors. Where a significant main effect or interaction was observed Bonferroni

post hoc assessment was used to identify where the differences occurred. DOMS was also analysed via linear mixed models with condition and time (baseline, 24 h and 48 h) set as fixed factors and participants were set as random factors, and Bonferroni post hoc assessment implemented where a significant main effect or interaction was observed. PAAS subscales (positive affect, negative affect, fatigue, and tranquillity) were compared using Friedman's non-parametric test. Where significant differences occurred between conditions or time (PRE and POST), Wilcoxon signed-rank pairwise comparisons identified where the differences occurred. Magnitude of differences were determined using Cohens *d* (calculated as test statistic divided by square root of sample number); small effect = 0.20 – 0.49, moderate effect = 0.50 – 0.79, and large effect = ≥0.80. Statistical analysis was conducted using SPSS (Version 26, Chicago, United States), with statistical significance set at $p \leq 0.05$.

4.4 Results

4.4.1 Young Adults

Side Effects and Adverse Events

There were no reported side effects, adverse or serious adverse events recorded during the study period.

Total Repetitions Completed

The number of repetitions completed for each protocol is presented in **TABLE 8.**

Perceptual Responses

A main effect of condition ($p < 0.001$) and exercise ($p < 0.001$) was observed for RPE **(FIGURE 10)**. Post hoc analysis revealed RPE was lowest during LL compared to LL-BFR ($p < 0.001$; $d = -1.5$) and ML-RE ($p < 0.001$; $d = -1.2$). Additionally, RPE was greater across all conditions during knee extension than leg press ($p < 0.001$; $d = 1.4$). A main effect of condition ($p < 0.001$) and exercise ($p < 0.001$) was observed for pain **(FIGURE 10)**. Post hoc analysis revealed pain was highest during LL-BFR than LL ($p < 0.001$; $d = 1.5$) and ML ($p = 0.002$; $d = 0.9$). Additionally, pain was greater across all conditions during knee extension than leg press ($p < 0.001$; $d = 1.3$). A condition by time interaction ($p = 0.003$) was observed for DOMS **(FIGURE 11)**. Post hoc analysis revealed DOMS was elevated at 24 h ($p < 0.001$; $d = 1.3 – 2.7$) and 48 h ($p \leq 0.014$; $d = 0.9 – 1.7$) from baseline for all conditions. DOMS at 24 h was lower following LL-RE compared to LL-BFR ($p < 0.001$; $d = -1.4$) and ML ($p = 0.001$; $d = 1.1$).

Affective Responses

Affective responses are presented in **TABLE 9.** Differences were observed for fatigue ($p = 0.036$). Post hoc analysis revealed fatigue increased from pre to post following ML-RE ($p = 0.017$; $d = 0.6$). Additionally, fatigue was greater post ML compared to post LL ($p = 0.028$; $d = 0.6$). Differences were observed for tranquillity ($p < 0.001$). Post hoc analysis revealed tranquillity decreased from pre to post for LL-BFR ($p = 0.003$; $d = -0.7$) and ML-RE ($p = 0.005$; $d = -0.7$).

Physiological Responses

Physiological responses are presented in **TABLE 10**. A main effect of condition ($p < 0.001$) was observed for HR_{mean}. Post hoc analysis revealed HR_{mean} was lowest during LL compared to LL-BFR ($p < 0.001$; $d = -1.3$) and ML ($p < 0.001$; $d = -1.0$). A main effect of condition ($p < 0.001$) was observed for HR_{peak}. Post hoc analysis revealed HR_{peak} was lowest during LL compared to LL-BFR ($p = 0.002$; $d = -0.9$) and ML ($p < 0.001$; $d = -1.2$). A main effect of exercise ($p = 0.048$) was observed for SBP. Post hoc analysis revealed SBP was higher across all conditions during knee extension than leg press ($p = 0.048$; $d = 0.5$). A main effect of condition ($p = 0.040$) was observed for DBP. Post hoc analysis revealed DBP was higher following LL-BFR compared ML ($p = 0.034$; $d = 0.7$). A main effect of condition ($p < 0.001$) and exercise ($p = 0.003$) was observed for RPP. Post hoc analysis revealed RPP was lowest during LL compared to LL-BFR ($p = 0.002$; $d = 0.9$) and ML-RE ($p < 0.001$; $d = -1.2$). Additionally, RPP was higher across all conditions during knee extension than leg press ($p = 0.003$; $d = 0.8$).

4.4.2 Older Adults

Side Effects and Adverse Events

One side effect was recorded during LL-BFR with a female participant who terminated exercise shortly after starting the 3rd set of knee extension due to feelings of tight thigh muscles which caused unease. The feeling of tight thigh muscles was relieved immediately following cuff deflation and the participant did not report any further issues. One adverse event occurred outside of the testing environment. A male participant developed superficial thrombophlebitis in his right leg a week after completing all study commitments. Specifically, the adverse

event occurred approximately three weeks after LL-BFR, two weeks following ML and one week following LL. The participant made a full recovery following four weeks of treatment. In consultation with the research teams' clinical expert, it was deemed this adverse effect was unlikely to be caused due to the exercise protocols completed in this study and the length of time in which the issue presented.

Total Repetitions Completed

The number of repetitions completed for each protocol is presented in **TABLE 8.**

Perceptual Responses

A main effect of condition ($p < 0.001$) and exercise ($p < 0.001$) was observed for RPE **(FIGURE 10)**. Post hoc analysis revealed RPE was lowest during LL compared to LL-BFR ($p < 0.001$; $d = -1.1$) and ML-RE ($p < 0.001$ $d = -1.6$). Additionally, RPE was greater across all conditions during knee extension than leg press ($p < 0.001$; $d = 1.4$). A main effect of condition ($p < 0.001$) and exercise ($p < 0.001$) was observed for pain **(FIGURE 10)**. Post hoc analysis revealed pain was highest during LL-BFR than LL ($p < 0.001$; $d = 1.4$) and ML ($p < 0.001$; $d = 1.0$). Additionally, pain was greater across all conditions during knee extension than leg press ($p < 0.001$; $d = 1.7$). A main effect of condition ($p = 0.002$) and time ($p < 0.001$) was observed for DOMS **(FIGURE 11)**. Post hoc analysis revealed DOMS was lowest following LL compared to LL-BFR ($p = 0.049$; $d = -0.6$) and ML ($p = 0.001$; $d = -0.8$). Additionally, DOMS across all conditions was elevated from baseline at 24 h ($p < 0.001$; $d = 1.4$) and 48 h ($p = 0.031$; $d = 0.6$) post exercise.

Affective Responses

Affective responses are presented in **TABLE 9.** Differences were observed for tranquillity (p = 0.001). Post hoc analysis revealed tranquillity increased from pre to post for ML (p = 0.002; d = 0.7).

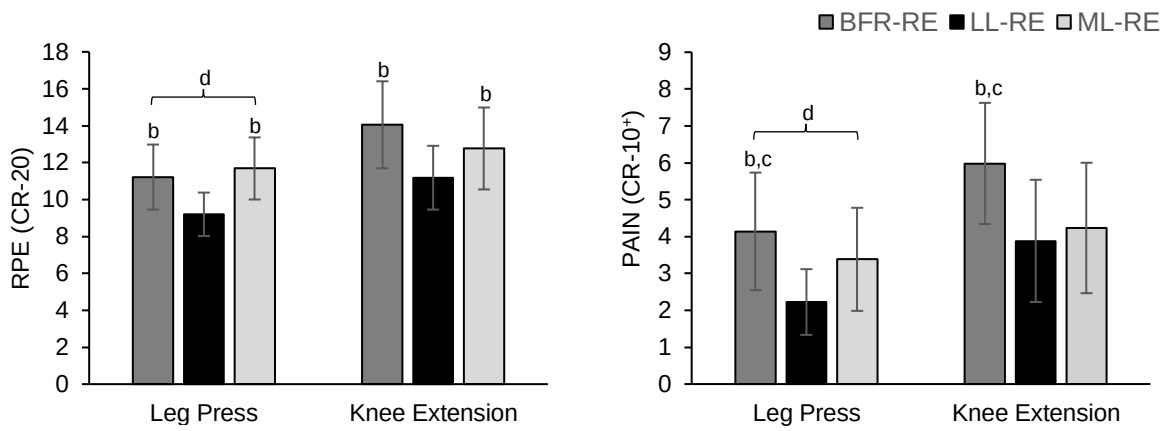
Physiological Responses

Physiological responses are presented in **TABLE 10**. A main effect of condition (p = 0.006) was observed for HR_{mean}. Post hoc analysis revealed HR_{mean} was highest during LL-BFR compared to LL (p = 0.014; d = 0.7) and ML (p = 0.020; d = 0.7). A condition by time interaction (p = 0.011) was observed for HR_{peak}. Post hoc analysis revealed HR_{peak} higher during LL-BFR than LL (p = 0.001; d = 0.9) and ML (p = 0.031; d = 0.7). Additionally, HR_{peak} for LL-BFR was greater during knee extension than leg press (p = 0.023; d = 0.7). A main effect of exercise (p = 0.037) was observed for SBP. Post hoc analysis revealed SBP was higher across all conditions during knee extension than leg press (p = 0.037; d = 0.5). A main effect of condition (p = 0.001) and exercise (p = 0.020) was observed for RPP. Post hoc analysis revealed RPP was lowest during LL compared to LL-BFR (p < 0.001; d = -0.9) and ML (p = 0.032; d = -0.6). Additionally, RPP was higher across all conditions during knee extension than leg press (p = 0.020; d = 0.5). A main effect of exercise (p = 0.014) was observed for PP. Post hoc analysis revealed PP was higher across all conditions during knee extension than leg press (p = 0.014; d = 0.6). A main effect of exercise (p = 0.014) was observed for PP. Post hoc analysis revealed PP was higher across all conditions during knee extension than leg press (p = 0.014; d = 0.6).

TABLE 8: Percentage (%) of repetitions completed.

	LL-BFR	LL	ML
Young Adults			
Leg Press	100 ± 0	100 ± 0	100 ± 0
Knee Extension	100 ± 0	100 ± 0	100 ± 0
Older Adults			
Leg Press	100 ± 0	100 ± 0	100 ± 0
Knee Extension	96 ± 13	100 ± 0	100 ± 0

Young Adults



Older Adults

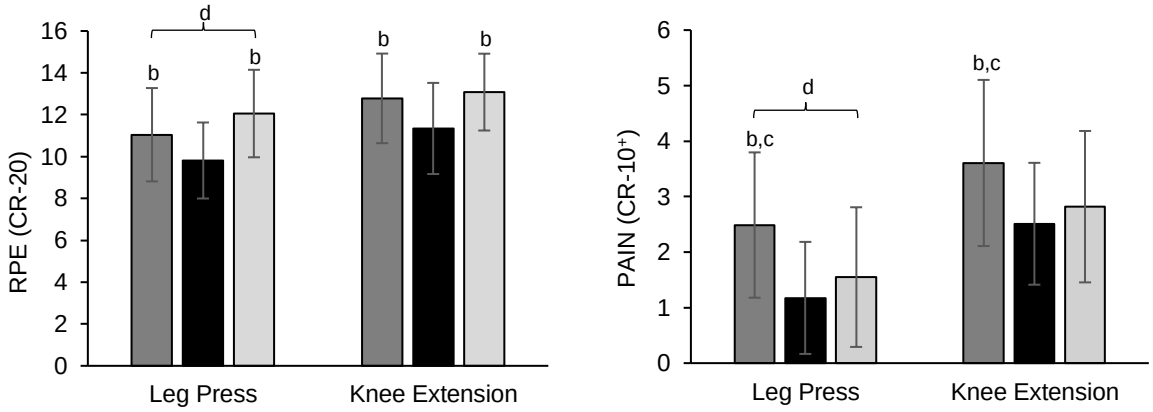


FIGURE 10: RPE and pain for leg press and knee extension during each condition. [a] Significantly different to LL-BFR, [b] significantly different to LL, [c] significantly different to ML, and [d] significantly different to knee extension.

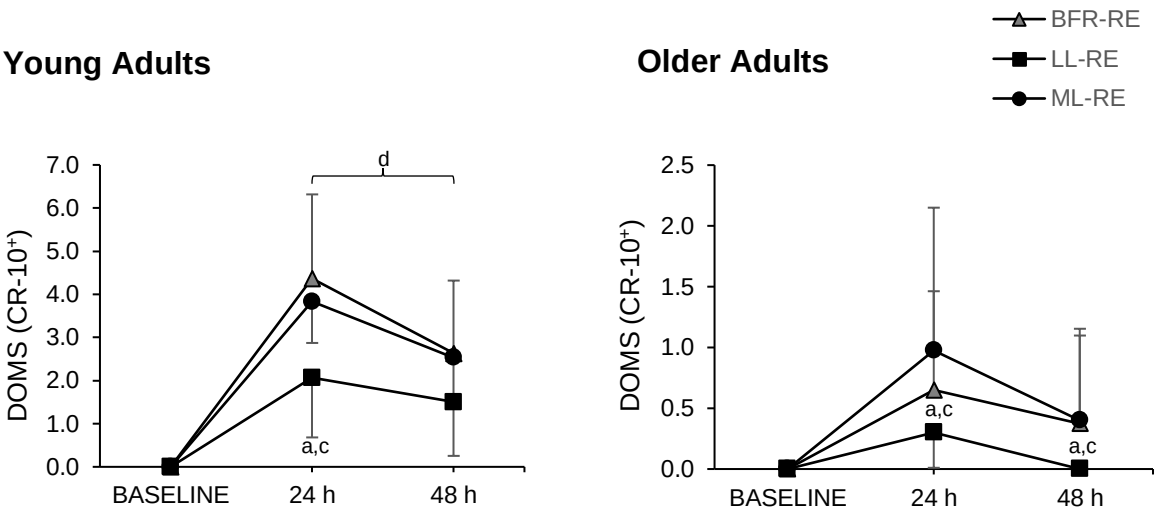


FIGURE 11: Delayed onset muscle soreness following LL-BFR, LL and ML. [a] Significantly different to LL-BFR, [b] significantly different to LL, [c] significantly different to ML, [d] significantly different to baseline.

TABLE 9: Affective response to LL-BFR, LL and ML.

	LL-BFR		LL		ML	
Young Adults						
PAAS (0 – 4)	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Positive affect	1.7 (1.3 – 2.0)	1.7 (1.3 – 2.0)	1.7 (1.7 – 2.0)	2.0 (1.65 – 2.0)	2.0 (1.7 – 2.0)	1.7 (1.5 – 2.0)
Negative affect	0.0 (0.0 – 0.15)	0.0 (0.0 – 0.3)	0.0 (0.0 – 0.3)	0.0 (0.0 – 0.15)	0.0 (0.0 – 0.5)	0.0 (0.0 – 0.85)
Fatigue	1.0 (0.3 – 1.3)	1.3 (1.0 – 1.65)	1.0 (0.85 – 1.7)	1.0 (0.7 – 1.0)	1.0 (0.3 – 1.3)	1.3 (1.0 -2.0) [b,d]
Tranquillity	2.3 (2.0 – 2.7)	1.7 (1.35 – 2.0) [d]	2.3 (2.0 – 2.85)	2.0 (1.5 – 2.15)	2.0 (1.7 – 2.5)	1.3 (1.3 – 1.85) [d]
Older Adults						
PAAS (0 – 4)	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Positive affect	1.7 (1.3 – 2.0)	1.7 (1.3 – 2.0)	1.7 (1.7 – 2.0)	2.0 (1.65 – 2.0)	2.0 (1.7 – 2.0)	1.7 (1.5 – 2.0)
Negative affect	0.0 (0.0 – 0.08)	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.4)	0.0 (0.0 – 0.0)
Fatigue	0.7 (0.0 – 1.0)	0.7 (0.3 – 1.07)	0.3 (0.225 – 0.7)	0.3 (0.0 – 0.7)	0.5 (0.3 – 1.0)	0.7 (0.0 – 1.07)
Tranquillity	2.7 (2.0 – 3.0)	3.0 (2.6 – 3.3)	2.85 (2.0 – 3.08)	3.0 (2.0 – 3.0)	2.7 (2.0 – 3.0)	3.0 (2.6 – 3.7) [d]

Data presented as 50^{th} (25^{th} – 75^{th}) percentiles. [a] Significantly different to LL-BFR, [b] significantly different to LL, [c] significantly different to ML and, [d] significantly different to Pre.

TABLE 10: Physiological Responses to leg press and knee extension during each condition.

Young Adults	LL-BFR	LL	ML
Leg Press			
HR_{mean}	113.6 ± 29.7 [b]	106.1 ± 25.6	115.0 ± 27.1 [b]
HR_{peak}	125.0 ± 31.6 [b]	118.6 ± 26.8	137.4 ± 30.9 [b]
SBP	149.3 ± 10.0 [d]	147.6 ± 16.5 [d]	151.3 ± 14.3 [d]
DBP	82.4 ± 6.2 [c]	82.9 ± 7.6	81.0 ± 8.0
MAP	104.7 ± 5.6	104.4 ± 7.9	104.5 ± 9.1
RPP	179.5 ± 55.6 [b,d]	166.6 ± 54.5 [d]	193.8 ± 53.7 [b,d]
PP	104.7 ± 5.6	104.4 ± 7.9	104.5 ± 9.1
Knee Extension			
HR_{mean}	120.0 ± 31.6 [b]	105.2 ± 21.7	114.3 ± 28.2 [b]
HR_{peak}	134.1 ± 37.0 [b]	119.3 ± 29.9	137.8 ± 31.6 [b]
SBP	155.7 ± 12.3	148.3 ± 14.3	155.4 ± 11.6
DBP	86.5 ± 7.5 [c]	82.0 ± 10.0	79.8 ± 6.3
MAP	109.6 ± 7.1	104.1 ± 10.7	105 ± 7.5
RPP	207.0 ± 68.0 [b]	175.9 ± 52.6	202.4 ± 57.5 [b]
PP	109.6 ± 7.1	104.1 ± 10.7	105.0 ± 7.5
Older Adults	**LL-BFR**	**LL**	**ML**
Leg Press			
HR_{mean}	86.0 ± 12.4 [b,c]	84.1 ± 11.5	84.2 ± 13.1
HR_{peak}	94.1 ± 13.2 [d]	92.8 ± 12.9	96.2 ± 15.3
SBP	144.6 ± 15.5 [d]	131.3 ± 16.2 [d]	139.7 ± 19.9 [d]
DBP	86.7 ± 9.3	82.9 ± 10.3	85.3 ± 11.9
MAP	106.0 ± 10.3	99.0 ± 11.7	103.4 ± 13.4
RPP	131.9 ± 26.9 [b,d]	117.2 ± 18.3 [d]	133.6 ± 32.9 [b,d]
PP	57.9 ± 11.7 [d]	48.4 ± 10.0 [d]	54.4 ± 14.5 [d]
Knee Extension			
HR_{mean}	87.6 ± 11.7 [b,c]	82.8 ± 11.1	82.6 ± 9.9
HR_{peak}	101.5 ± 14.8 [b,c]	92.6 ± 11.9	94.4 ± 11.4
SBP	144.3 ± 21.7	142.5 ± 16.9	145.6 ± 14.2
DBP	86.2 ± 10.5	84.3 ± 9.9	84.4 ± 11.0
MAP	105.5 ± 12.3	103.7 ± 11.2	104.8 ± 10.0
RPP	145.6 ± 28.1 [b]	131.3 ± 21.2	134.7 ± 24.0 [b]
PP	58.1 ± 18.8	58.3 ± 12.7	61.2 ± 14.6

[a] Significantly different to LL-BFR, [b] significantly different to LL, [c] significantly different to ML, and [d] significantly different to knee extension.

4.5 Discussion

The purpose of this investigation was to explore the perceptual, affective, and physiological responses to lower-body resistance exercise when performed at LL-BFR, LL and ML in young and older adults. The main findings of the investigation indicate (1) LL-BFR elevates pain greater than LL and ML, (2) despite an increase in pain during exercise, LL-BFR did not elicit a negative affective response, (3) LL-BFR increased HR responses and myocardial workload compared to LL, which was comparable to ML and, (4) RPE and pain were higher during knee extension compared to leg press in all resistance exercise sessions, which may be further elevated by LL-BFR.

An increase in pain with the application of BFR to low-load resistance exercise is extremely consistent within the literature indicating the additional stress of BFR (Spitz et al., 2020). The addition of BFR when resistance exercising limits the recovery of fatigue-related metabolites and contractile function within the inter-set rest periods causing development of peripheral fatigue and increased perception of pain (Husmann et al., 2018). Many previous studies have compared ratings of pain between BFR with low-load resistance exercise and high-load resistance exercise without BFR in young adults. Freitas et al., (2019) reported no differences in pain during leg press and knee extension resistance exercise when performed with BFR following standard protocol (30-15-15-15 repetitions at 20% 1RM) and at high load without BFR (4 sets of 10 repetitions at 70% 1RM). Miller et al., (2020) and Soligon et al., (2018) report similar conclusions, though both studies used a high load resistance exercise protocol that was greater in load (80% 1RM) and lower in volume (3 sets of 10 repetitions) and BFR

resistance exercise protocol that was greater in load (30% 1RM). Our conflicting observation is most likely due to different exercise protocols used for the resistance exercise without BFR condition with the present study using moderate load (60% 1RM) compared to previous studies using high load (70 – 80%) as higher loads will require greater muscular exertion which can elevate pain perception (Hollander et al., 2017). Many individuals with low resistance exercise experience may find high-load resistance exercise challenging. This is evident in previous studies where participants failed to complete all programmed repetitions for the high-load resistance exercise condition leading to near maximal RPE (Freitas et al., 2019; Miller et al., 2020). Therefore, the inclusion of moderate-load (60% 1RM) resistance exercise protocols in the present study was an attempt to improve the comparisons made between resistance exercise with and without BFR for low resistance exercise experienced individuals. To the author's knowledge, no previous study has compared BFR-RE with resistance exercise without BFR at loads ≥60% 1RM in older adults. This study has shown the pain response of older adults during LL-BFR may be less severe than young adults, but the pain experienced was still greater than during ML to a similar magnitude.

Elevated pain and metabolic accumulation are thought to contribute to a reduced affective response with BFR compared to non-BFR during walking (Mok et al., 2020). A limitation of the present study was the exclusion of the affective response during exercise. Immediately post exercise, mood status assessed via Brunel Mood Scale has shown to be negatively affected by BFR through reduced vigour and increased fatigue following resistance (Silva et al., 2018) and aerobic (Silva et al., 2019) exercise in athletic groups. The present study did not observe

an increase of fatigue following LL-BFR. Differing observations may be caused by an increased resistance load employed (Silva et al., 2018) and longer exercise duration (Silva et al., 2019) leading to elevated levels of fatigue. The affective response to exercise is an important factor determining future physical activity behaviour (Rhodes & Kates, 2015) and infers the acceptability of an exercise modality (Devereux-fitzgerald et al., 2016). Individuals who experience improvements in affect, and low fatigue from exercise report more positive attitudes, exercise self-efficacy and intentions to exercise three months later (Kwan & Bryan, 2010; Mitropoulos et al., 2020). Adherence to exercise programmes is a major barrier for practitioners prescribing exercise to older adults (Room et al., 2017) and adherence to exercise programmes will maximise muscular adaptations (Pisters et al., 2010; Van Gool et al., 2005). Prior to this study, the effect of BFR-RE on affective parameters following exercise in older adults had not been explored. Our findings of a comparable affective response between LL-BFR, LL and ML may encourage practitioners to utilise BFR-RE with this population.

The present study demonstrated an increased physiological demand with the addition of BFR to low-load resistance exercise. Previous studies have consistently shown the application of BFR to low-load resistance exercise augments HR and blood pressure responses (Neto et al., 2017). This may be contributed by the reduced blood flow during muscular exertion that augments metabolic accumulation and pain and influences the pattern of muscle recruitment which increases the exercise pressor reflex resulting in an enhanced autonomic cardiovascular response (Manini & Clark, 2009; Spranger et al., 2015).

More debated is the extent this increase in physiological response compares with resistance exercise without BFR performed with higher loads. Some studies conclude physiological responses to BFR resistance exercise exceed high-load resistance exercise without BFR (Domingos & Polito, 2018; Scott et al., 2018) and others report comparable or lower responses (Pinto et al., 2018; Poton & Polito, 2014). Physiological responses reported in the BFR literature are highly variable likely due to differing measurement techniques, exercise protocols and sample populations between studies. Importantly, the observed increases in HR and blood pressure responses are consistently within the normal range expected during exercise (Fletcher et al., 2001).

An interesting finding in the present study was an increase in perceptual response during knee extension compared to leg press, which may be exaggerated with BFR. This disagrees with finding from (Scott et al., 2018) who reported an increase in RPE with leg press than knee extension. Conflicting observations may be due to the different exercise protocols between studies, with (Scott et al., 2018) utilising lower exercise volume of 1 set of 20 repetitions followed by 2 sets of 15 repetitions for both leg press and knee extension. However, against studies who have employed similar exercise protocols to the present study, trends of increased RPE and pain during knee extension compared to leg press performed with BFR and without BFR were observed (Freitas et al., 2019; Miller et al., 2020). The discrepancy in perceptual response between leg press and knee extension could be due to physiological changes caused by mechanical differences. More volume of exercise can be completed with large muscle group exercises (e.g. leg press) compared with smaller muscle group exercises (e.g. knee extension) at

the same relative intensity (Shimano et al., 2006; Tibana et al., 2011). This may be due to asynchronous motor unit recruitment during submaximal exercise which serves to delay fatigue (Shimano et al., 2006). Thereby, individuals may tolerate leg press to a greater degree than knee extension at a set exercise load when high exercise volume is performed. Why BFR may exaggerate the increase in perceptual response to knee extension compared to leg press is unclear. Although speculative, the dynamic hip extension-flexion action during leg press may facilitate venous flow with BFR which could limit blood pooling and metabolic accumulation proximal to the restrictive cuff lessening the perceptual response compared to static hip action during knee extension. Furthermore, the contribution of hip extensor muscles during leg press may not be significantly affected by the BFR stimulus and thus less susceptible to the accumulation of metabolic stress associated with BFR.

The study is not without limitations. First, the use of Brzycki equation to predict 1RM (Brzycki, 1993) rather than prescribing exercise intensity from a true 1RM may have accounted for some variation within this study. Second, we recognise that although participants completed the conditions in a randomised order, we cannot dismiss a repeated-bout effect that could contribute to altered perceptual responses to resistance exercise. RPE and pain have shown to subside after repeated sessions of resistance exercise, suggesting an adaptive effect to psychological markers (e.g. sense of effort and pain) that facilitates greater tolerance (Chen et al., 2010; Martín-Hernández et al., 2017). Third, we acknowledge that participants recruited for this study were all physically active and interested in exercise. Clinical populations with musculoskeletal disorders

and/or muscle weakness may respond to the exercise conditions differently to those included in the present study.

In conclusion, these data suggest BFR with low-load resistance exercise is less tolerable than resistance exercise without BFR through elevated pain, though the affective and physiological responses are like that of moderate-load resistance exercise without BFR. This study also demonstrates exercise selection must be carefully considered in BFR prescription as the type of lower body resistance exercise can have a substantial effect on the perceptual response during exercise. These findings provide interesting insights into the tolerability of BFR-RE in young and older adults and has practical relevance to practitioners, especially if they are considering implementing BFR-RE with individuals who display low motivation or poor adherence to exercise programmes. BFR-RE can be useful to both young and older adults to initiate beneficial muscular adaptations, though we suggest caution if implementing BFR-RE particularly with individuals who are less able to tolerate elevated levels of pain.

5 Test-Retest Reliability of Physical Function Test Battery for Patients with Intermittent Claudication

5.1 Abstract

Purpose: The study aims to evaluate the test-retest reliability of a test battery to assess physical function in patients with IC.

Methods: Seventeen men with stable IC were recruited. The test battery consisted of the ABPI, 6MWT, unilateral isometric knee extension maximal voluntary torque (MVT) and Vastus Lateralis muscle thickness (VL-MT). A single investigator conducted the tests for each patient on two separate testing sessions (T1 and T2) 5 – 7 days apart.

Results: Excellent overall reliability was observed for ABPI (ICC = 0.96, 95% LOA = 0.11, SEM = 0.04), 6MWT (ICC = 0.97, 95% LOA = 41.6 m, SEM = 17.3 m), MVT (ICC = 0.94, 95% LOA = 24.7 N·m, SEM = 9.96 N·m), and VL-MT (ICC = 0.92, 95% LOA = 2.85 mm, SEM = 0.75 mm). Analysis derived from reliability data indicates a change of 0.08 for ABPI, 35.5 m for 6MWT, 17 N·m for MVT, and 1.5 mm for VL-MT is required to be interpreted as the minimum ‘’likely’’ change (76% chance).

Conclusion: The test battery provides a reliable assessment of physical function in patients with IC and can be widely used to evaluate the effects of exercise programmes. For the individual, changes in ABPI, 6MWT, MVT and VL-MT greater than the minimum likely change are less influenced by day-to-day variation associated with the test.

5.2 Introduction

IC is a common and debilitating symptomatic presentation of peripheral arterial disease (PAD) due to atherosclerotic occlusive disease (M. Gerhard-Herman et al., 2017). IC is associated with reduced exercise performance and poor lower-extremity muscle mass and strength (Leeper et al., 2013; Mcdermott et al., 2004; Mcdermott et al., 2004). Supervised exercise programmes are recommended for patients with IC (Gerhard-Herman et al., 2017). To objectively describe the outcomes of an exercise programme, practitioners may wish to adopt a test battery that assesses PAD severity, walking performance, and lower-extremity muscles size and strength.

The ABPI is a non-invasive test for the screening, diagnosis, and haemodynamic monitoring of PAD (Gerhard-Herman et al., 2017). A low ABPI (<0.90) defines the presence of PAD with lower ABPI indicating greater hemodynamically significant PAD (Aboyans et al., 2012). ABPI has shown good to excellent inter- and intra-day, inter- and intra-rater reliability in PAD (Casey et al., 2019; de Graaff et al., 2001). The 6MWT is used to evaluate walking performance in patients with IC (Mcdermott et al., 2009; Nordanstig et al., 2014). The 6MWT is conducted in a corridor, is easy to perform, and reflects normal walking (Mcdermott et al., 2014). 6MWT has shown excellent intraday test-retest reliability in patients with IC (Sandberg et al., 2019). Change in the 6MWT predicts risk for mortality and mobility loss in patients with PAD (McDermott et al., 2011). B-mode ultrasound imaging is a valid tool to assess muscle size (Nijholt et al., 2017). VL-MT, defined as the distance between the superficial and deep aponeurosis is easily determined with ultrasound imaging and has shown highly correlated to cross-

sectional area of muscle (Abe et al., 1997). B-mode ultrasound imaging of VL-MT is reliable (English et al., 2012; Nijholt et al., 2017), though this has not been investigated in patients with IC. Isokinetic dynamometry is the gold standard for measuring muscle function (Drouin et al., 2004). An isokinetic dynamometer can operate in an isometric mode to measure MVT in a predetermined position without limb movement allowing a safe maximal effort to be performed (Alvares et al., 2015). Isometric MVT are a well-established technique to assess lower-extremity strength in PAD (Mcdermott et al., 2009; Mcdermott et al., 2004; Scott-Okafor et al., 2001)**.** Isometric MVT has previously shown excellent reliability (Drouin et al., 2004; van Driessche et al., 2018), though this has not been determined specifically in patients with IC.

For this this physical function test battery to be useful for practitioners, it is important to assess the test-retest reliability and determine the smallest worthwhile change in test scores for the individual. The aim of this study was to evaluate the interday test-retest reliability of the ABPI, 6MWT, MVT, and VL-MT in people with intermittent claudication. To provide a practical context to test-retest reliability data, the study will present changes in ABPI, 6MWT, VL-MT and MVT to interpret the probability of a true change using the analysis approach of Hopkins (Hopkins, 2004).

5.3 Methods

Patients

The study was approved by Yorkshire and The Humber – Leeds West Research Ethics Committee (REC reference: 20/YH/0039; IRAS project ID: 260419) and

was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Seventeen men with stable IC were recruited from the Sheffield Vascular Institute of Sheffield Teaching Hospitals NHS Foundation Trust. Patients were excluded from the study if: ABPI was >0.89, patients presented PAD related symptoms of rest pain, skin ulcers or gangrene, and walking is limited by a non-PAD condition or cannot walk without a walking aid. All patients were informed of the experimental procedures and associated risks of the study before giving written informed consent.

Study Design

A single trained and experienced investigator conducted all the tests for each participant using standard operating procedures on two separate testing sessions (T1 and T2). The tests were performed in a systematic order: (1) VL-MT, (2) ABPI, (3) MVT, and (4) 6MWT. Order was chosen in attempt to minimise the effects of the previous test influencing the subsequent test. The testing sessions were conducted at the same time of day for each patient, with T1 and T2 separated by 5 – 7 days.

Vastus Lateralis Muscle Thickness

VL-MT was assessed via B-mode ultrasonography in accordance with standardised procedures (Ticinesi et al., 2018). Both legs of the patient were measured at T1 and T2. Patients were asked to lie on a hospital bed with the knee fully extended and to maintain a resting condition throughout the test. The investigator waited 15 minutes before VL-MT measurement to allow fluid shifts to occur. The midpoint between the greater trochanter and lateral epicondyle and

the midpoint between the medial and lateral edges of the vastus lateralis provided the reference point for ultrasound imaging. A 14 MHz probe (L14-4, Sonimage MX1, Konica Minolta, Tokyo, Japan) was longitudinally oriented at the reference point. Generous amounts of surface gel were used to promote acoustic coupling while avoiding dermal deforming. To measure VL-MT clear image of the superficial and deep aponeurosis were obtained and recorded. All images were analysed using computer software (ImageJ, U.S. National Institutes of Health, Maryland, USA). VL-MT was determined as the mean distance between the superficial aponeurosis and the deep aponeurosis at three different positions (left, middle, right) of the picture.

Ankle Brachial Pressure Index

ABPI was assessed using the gold standard Doppler ultrasound technique (Aboyans et al., 2012) and was recorded for each leg. Patients were asked to lie and maintain a resting position. The investigator allowed 10 minutes before assessing systolic blood pressure at the arms (brachial arteries) and ankles (dorsalis pedis and posterior tibial arteries). A pneumatic cuff was placed around the upper arm with the lower edge of the cuff approximately 2 cm above the antecubital fossa and around the lower leg with the lower edge of the cuff approximately 2 - 4 cm above the ankle medial malleolus. A handheld vascular Doppler device (HI-Dop vascular Doppler, Ana Wiz, Surrey, UK) was positioned over the brachial, posterior tibial and dorsalis pedis arteries. The pneumatic cuff was inflated until Doppler flow signal was lost and the systolic blood pressure was determined by the first Doppler flow signal while deflating the cuff from a suprasystolic level. Systolic blood pressure was measured sequentially for the

brachial, dorsalis pedis and posterior tibial arteries. The ABPI was calculated by dividing the higher of the dorsalis pedis or posterior tibial pressure of each leg by the higher of the right or left brachial artery pressure.

Maximal Voluntary Torque

Unilateral isometric knee extension MVT was performed for both legs using the Cybex Humac Norm Isokinetic Extremity System (Computer Sports Medicine Incorporated, Massachusetts, USA). Patients were seated with the knee and hip joints at 90° flexion, with the waist and thigh strapped to limit extraneous movements. Patients first performed a warm-up consisting of 5 repetitions of 3 second submaximal isometric knee extensions. Following this, patients were asked to perform three MVT lasting 3 seconds with minimum 60 seconds rest between each effort. During the determination of MVT, patients received visual feedback of the force signal and strong verbal encouragement to motivate maximal efforts. The highest peak force of the three MVT efforts were used for analysis.

Six-minute Walk Test

The 6MWT was performed following the American Thoracic Society guidelines (Enright, 2003). The 6MWT was performed indoors, in a long, flat, and straight corridor on hard flooring with the walking circuit set at 20 m in length. Patients were seated at the starting position for 5 minutes before starting the test to ensure the recovery of the previous activity. Patients were asked to complete as many walking circuits as possible in 6 minutes. Patients were informed that they could rest at any point during the 6MWT. During the 6MWT, patients were given

standardised phrases of verbal encouragement at each minute of the test. The total distance covered in the 6-minute period was recorded and used for analysis.

Statistical Analysis

The test-retest reliability of VL-MT, ABPI, MVT and 6MWT was assessed through several statistical analyses following the guidelines of Atkinson and Nevill (1998). Shapiro-wilk test of normality confirmed normal distribution of VL-MT and ABPI and a non-normal distribution of MVT and 6MWT. Additionally, the mean difference between T1 and T2 followed a normal distribution for all variables. Bland–Altman plots (Bland & Altman, 1986) were compiled to present systematic and random error trends for all variables. Systematic bias between T1 and T2 was assessed via a paired *t*-test for VL-MT and ABPI and a related-samples Wilcoxon Signed Rank test for MVT and 6MWT. Statistical significance was set at $p \leq 0.05$. Absolute reliability was assessed by standard error of measurement (SEM) and 95% limits of agreement (95% LOA). Relative reliability was assessed by intraclass correlation coefficients (ICC) with 95% confidence intervals. To provide a practical context to test-retest reproducibility data, we proposed hypothetical changes in VL-MT, ABPI, MVT and 6MWT to interpret probability of change using the analysis approach of Hopkins (Hopkins, 2004). The analysis determined the probability of ‘’decrease’’, ‘’no change’’ and ‘’increase’’ to a change in relation to the smallest worthwhile change (0.2 * between-participant SD). The analysis also identified the minimum magnitude of change in VL-MT, ABPI, MVT and 6MWT that is a likely change (76% probability).

5.4 Results

Patients recruited consisted of older (69 ± 9.8 years; stature = 175.6 ± 6.8; body mass = 82.3 ± 10.8 kg; body mass index = 26.7 ± 3.2 kg·m^2), symptomatic white men reflecting moderately severe PAD (ABPI = 0.68 ± 0.13). 82% of patients were previous smokers and 24% were current smokers.

A significant systematic bias was evident for 6MWT with T2 higher than T1 (4%), and a trend approaching significance of systematic bias for MVT with T2 lower than T1 (-3.5%) (**TABLE 11**). Systematic bias between T1 and T2 was near absent for VL-MT (-1%) and ABPI (1%) (**TABLE 11**). The 95% LOA for ABPI, 6MWT, MVT, and VL-MT are presented in the Bland-Altman plots (**FIGURE 12**). Reliability data is presented in **TABLE 12**. ICC indicate excellent agreement between T1 and T2 for all variables. The SEM was used to calculate the probabilities of a change in relation to the smallest worthwhile change using the approach of Hopkins (2004) (**TABLE 13**). This indicated a change of 0.08 for ABPI, 35.5 m for 6MWT, 17 N·m for MVT, and 1.5 mm for VL-MT is required to be interpreted as a likely beneficial change (76% chance).

TABLE 11: Mean (± SD) of test scores included in the test battery.

Variable	Test 1	Test 2	Bias ± SD	*p*
ABPI	0.79 ± 0.20	0.79 ± 0.20	-0.01 ± 0.06	0.38
6MWT (m)	382.9 ± 88.5	396.7 ± 90.7	-13.8 ± 21.2	0.03
MVT (N·m)	129.3 ± 34.3	124.7 ± 36.0	4.59 ± 12.6	0.06
VL-MT (mm)	21.5 ± 3.8	21.3 ± 3.6	0.22 ± 1.45	0.39

TABLE 12: Inter day reliability of physical function test battery.

Variable	95% LOA (±)	SEM	ICC
ABPI	0.11	0.04	0.96 [0.91, 0.98]
6MWT (m)	41.6	17.3	0.97 [0.92, 0.99]
MVT (N·m)	24.7	9.96	0.94 [0.88, 0.97]
VL-MT (mm)	2.85	0.75	0.92 [0.85, 0.96]

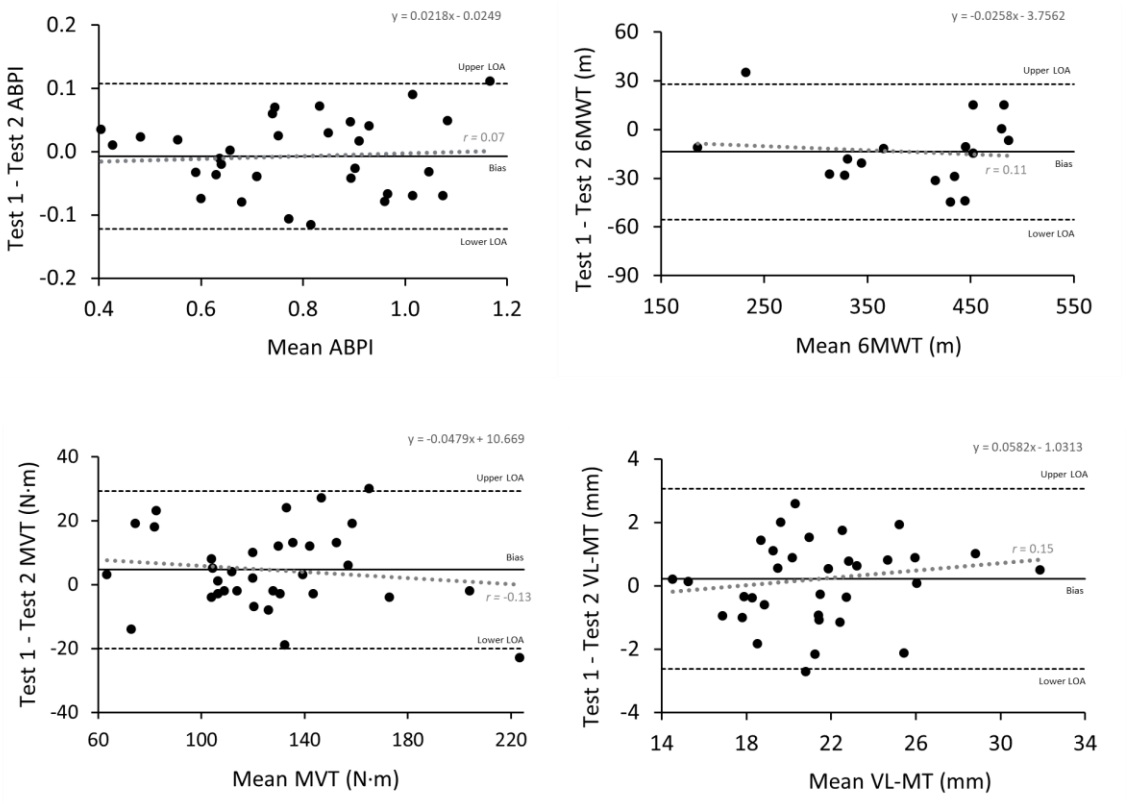


FIGURE 12: Bland-Altman plot of the ABPI, 6MWT, isometric knee extension MVT and VL-MT. The solid line represents the bias and dashed line represents the 95% limits of agreement.

TABLE 13: Probability of hypothetical changes in test scores in the physical function test battery.

Variable	Change in value	Probability of decrease (%)	Probability of no change (%)	Probability of increase (%)
ABPI	0.05	6 Unlikely, probably not	37 Possibly, may (not)	57 Possibly, may (not)
	0.10	1 Very unlikely	14 Unlikely, probably not	85 Likely, probable
	0.15	0 Most unlikely	3 Very unlikely	97 Very likely
6MWT (m)	20	7 Unlikely, probably not	40 Possibly, may (not)	53 Possibly, may (not)
	40	2 Very unlikely	17 Unlikely, probably not	81 Likely, probable
	60	0 Most unlikely	5 Very unlikely	95 Likely, probable
MVT (N·m)	10	12 Unlikely, probably not	30 Possibly, may (not)	58 Possibly, may (not)
	20	3 Very unlikely	15 Unlikely, probably not	82 Likely, probable
	30	1 Very unlikely	5 Unlikely, probably not	94 Likely, probable
VL-MT (mm)	1	6 Unlikely, probably not	34 Possibly, may (not)	60 Possibly, may (not)
	2	1 Very unlikely	11 Unlikely, probably not	88 Likely, probable
	3	0 Most unlikely	2 Very unlikely	98 Very likely

5.5 Discussion

The results in this study indicate excellent test-retest reliability for ABPI, 6MWT, MVT, VL-MT in patients with IC. To provide a practical context to the reliability data, the study identified the smallest magnitude of change in ABPI, 6MWT, MVT, and VL-MT required to be considered as a likely beneficial change (≥76% chance). Such information could be useful for practitioners interpreting changes in ABPI, 6MWT, MVT, and VL-MT in patients with IC following exercise programmes.

The present study obtained measurements of ABPI using the gold standard Doppler ultrasound technique and observed excellent agreement between T1 and T2 with ICC of 0.96 [0.91, 0.98]. This finding is comparable to that previously observed in patients with PAD displaying varying clinical stages (i.e. asymptomatic, IC, rest pain, ulcers, and gangrene) with ICC of 0.89 (de Graaff et al., 2001), in patients with suspected PAD with ICC of 0.94 [0.91 – 0.95] (Ichihashi et al., 2020) and a mix of patients with suspected PAD and healthy adults with ICC of 0.89 [0.84-0.92] (Aboyans et al., 2008). The observed systematic bias of -0.01 and 95% LOA of ±011 is consistent to the systematic bias of -0.01 and 95% LOA of ±0.18 reported previously from measurements of patients with suspected PAD (Ichihashi et al., 2020). However, a larger systematic bias of -0.06 and 95% LOA of ±0.22 has been observed previously (Aboyans et al., 2008). The increased error may be explained by their large sample size and their mixed population sample of patients with suspected PAD and healthy adults that increased the range of ABPI measurements. Nevertheless, the systematic bias and random error of ABPI using Doppler ultrasound is acceptable. In clinical

practice, a change of >0.15 in ABPI is generally accepted as clinically significant providing there is supporting evidence of hemodynamic improvement or deterioration (Norgren et al., 2007). To suggest a successful intervention, an increase of 0.10 in ABPI has been recommended as objective criteria (Rutherford, 1996). The present study somewhat affirms this as our findings suggest the smallest magnitude of change required to detect a likely beneficial change (76% chance) in ABPI is 0.08, and a change of 0.14 in ABPI is required to have a very likely beneficial change (>95% chance).

The 6MWT distance covered in the present study (382.9 ± 88.5 m) is comparable to the 397.9 ± 80.2 m observed previously which measured 100 patients with IC (Sandberg et al., 2019). The present study observed excellent agreement of the 6MWT between T1 and T2 with ICC of 0.97 [0.92, 0.99], which is consistent with previous studies in patients with IC with ICC of 0.95 [0.94, 0.97] (Sandberg et al., 2019), chronic heart failure with ICC of 0.90 [0.63, 0.96] (Uszko-Lencer et al., 2017), and knee osteoarthritis with ICC of 0.93 [0.77, 0.97] (Dobson et al., 2017). Despite excellent agreement, a significant systematic bias was observed with 6MWT distance higher in T2 than T1 (p = 0.03), of which 76% of patients performed better in T2. The improved performance in the 6MWT in T2 may be contributed to a learning effect that influenced the pace of walking or improved tolerance to walking following T1. However, the mean bias in the presented study is 13.8 ± 21.2 m and only 18% of patients improved 6MWT distance by ≥30 m. While this has not been observed previously in patients with IC (Sandberg et al., 2019), a learning effect of 31 m has been observed in patients with chronic heart failure with 40% of the patients increasing their walk distance in the retest

by >39.4 m (Uszko-Lencer et al., 2017). The present study identified a change of 35.5 m in 6MWT distance is required to detect a likely beneficial change (76% chance) and a change of >60 m to detect a very likely change (>95% chance). Prior to this study, the minimal detectable change of 6MWT test in patients with IC was determined as 46 m (Sandberg et al., 2019), which is similar to the 95% LOA of ±41.2 m observed in the present study. Additionally, the minimal clinically important difference in 6MWT distance, which represents the smallest threshold change in an outcome measure that is perceived beneficial to the patient has been reported in patients with IC (Gardner et al., 2018). After 3 months of exercise intervention, small (5%), moderate (25%), and large (40%) clinically important changes in the 6MWT distance were found to be at 12 m, 32 m, and 34 m, respectively (Gardner et al., 2018).

The use of isokinetic dynamometers is considered the gold standard to measure muscle function in clinical practice and research settings (Drouin et al., 2004). The present study used the Cybex Humac Norm System to assess isometric MVT which has shown excellent inter-machine reliability with the Biodex System 3 Pro (Alvares et al., 2015). The present study observed excellent agreement between T1 and T2 with ICC of 0.94 [0.88, 0.97]. This is comparable to the ICC of 0.97 observed in older adults (van Driessche et al., 2018). However, the present study observed a trend approaching significance of significant bias with MVT lower in T2 than T1 (p = 0.06). Therefore, the reliability of this test may be improved with prior familiarisation. While a significant difference between T1 and T2 has not been previously observed, the 95% LOA of ±24.7 is comparable to the 95% LOA of ±16% previous observed in older adults (van Driessche et al., 2018). The

present study identified a change of 17 N·m in MVT is required to detect a likely beneficial change (76% chance) and >30 N·m change in MVT to a very likely change (>95% chance). To improve the confidence in interpretation of an actual change in MVT, improved reliability would be required.

The VL-MT in patients with IC (21.5 ± 3.8 mm) is comparable to the 19.8 ± 2.4 measured in older adults without PAD of similar age (Strasser et al., 2013). The present study's ICC of 0.92 [0.85, 0.96] for VL-MT are comparable to the ICCs of 0.85 and 0.96 [0.90 – 0.98] in older adults (Raj et al., 2012; Strasser et al., 2013), ICCs of 0.88 in patients with knee osteoarthritis (Staehli et al., 2010), and ICCs of 0.95 in young adults (Strasser et al., 2013). Furthermore, a near absent systematic bias of 0.22 mm and 95% LOA of ±2.85 mm is consistent with the systematic bias of 0.0 cm and 95% LOA of ±0.3 cm reported previously (Staehli et al., 2010). The use of ultrasound to quantify muscle has shown to be reliable in older (Nijholt et al., 2017) and younger adults (English et al., 2012). This also extends to clinical populations, despite the possible increased difficulty to obtain quality ultrasound images due to echogenicity and reduced definition of muscle (Nijholt et al., 2017). It was identified that 1.5 mm change in VL-MT is the smallest magnitude of change required to detect a likely beneficial change (76% chance) in patients with IC. Any changes below this would decrease the confidence in interpretation leading to uncertainty of the true effect following an intervention.

A limitation to the study is the relatively small sample size. A larger sample size would reduce the random error of measurement that can make the mean of the measurement different for each test as random errors of the measurement can

cancel out when more data are included together for calculation of the mean (Hopkins, 2000). Furthermore, a larger sample would provide greater precision of estimates of ICC (Atkinson & Nevill, 1998). Nevertheless, the reliability of ABPI, 6MWT, MVT and VL-MT presented here are comparable to previous studies in other populations. Additionally, the inclusion of only white men in the present study is not representative of the PAD population (Fowkes et al., 2017) thereby limits the generalisability of these results to women and other ethnic groups with PAD.

In conclusion, the physical function test battery to assess PAD severity, walking performance, and lower-extremity muscles size and strength using ABPI, 6MWT, VL-MT of vastus lateralis using B-mode ultrasound imaging and unilateral isometric knee extension MVT has excellent overall reliability. However, a learning effect may be apparent in the 6MWT and unilateral isometric knee extension MVT which may require prior familiarisation when using to assess outcomes of an exercise programme. The study has provided probabilities of changes in test scores and practitioners can be confident a change of 0.08 for ABPI, 35.5 m for 6MWT, 17 N·m for MVT, and 1.5 mm for VL-MT as a result of an exercise programme are likely changes and less influenced by day-to-day variation with the test. This physical function test battery can be used with confidence by practitioners when interpreting changes in ABPI, 6MWT, MVT and VL-MT following an exercise programme in patients with IC.

6 Low-Load Resistance Exercise with Blood Flow Restriction for Patients with Intermittent Claudication: A Randomised Controlled Feasibility Study

6.1 Abstract

Purpose: IC is a common and debilitating symptom of PAD, resulting in significant reduction in exercise performance and QoL. Supervised exercise programmes are recommended as part of first-line therapy but have poor uptake and compliance due to pain during walking exercise. BFR-RE has shown to induce hypertrophy, strength and muscular endurance, enabling improved exercise performance. The study aim was to explore safety, feasibility and preliminary efficacy of BFR-RE in patients with IC.

Methods: Thirty patients with stable IC completed an 8-week lower-body resistance exercise programme of two sessions a week (16 sessions) and were randomly allocated in two groups (1) low-load with BFR (LL-BFR, n = 15) and (2) low-load without BFR (LL, n = 15). Patients unable to perform exercise and those with critical limb threatening ischemia were excluded.

Results: There were no adverse events. Completion rates (LL-BFR = 93%, LL = 87%) and exercise adherence (LL-BFR = 78.3%, LL = 83.8%) were high. Visual analogue scales for enjoyment, tolerance and difficulty were positive and similar between the two groups. A large clinically important improvement (≥35.5 m) in walking (six-minute walk test) was achieved in 86% of patients in LL-BFR but only 46% of patients in LL.

Conclusion: BFR-RE is a safe, feasible, enjoyable, and potentially efficacious mode of exercise to improve exercise performance in patients with IC.

6.2 Introduction

PAD is an atherosclerotic cardiovascular disease that describes hardened, narrowed, or obstructed arteries that supply to the lower extremities by atheroma (Gerhard-Herman et al., 2017). The prevalence of PAD rises sharply with age, affecting approximately 13% of adults >50 years old (Crawford et al., 2016). Exposure to cardiovascular risk factors initiates the pathophysiological processes of inflammation and vascular dysfunction which contributes to the development and severity of PAD and the subsequent limb ischemia experienced (Hamburg & Creager, 2017). The consequences of chronic limb ischemia are (1) endothelial dysfunction that impairs vasodilator function, hyperaemic response and arterial remodelling, (2) mitochondrial dysfunction that impairs energy production and oxygen unitisation, and increases reactive oxygen species, and (3) adverse skeletal muscle remodelling of reduced muscle mass, capillary-to-fiber ratio and capillary contacts to type I and type II muscle fibers (Askew et al., 2005; Hamburg & Creager, 2017). The most common symptomatic presentation of PAD is IC, which describes cramp-like leg pain that is consistently induced by walking and relieved by rest (Gerhard-Herman et al., 2017). IC occurs due to an impaired ability to increase blood flow and oxygen delivery to sufficiently match the metabolic demands of leg muscles during exercise (Morley & Sharma, 2018). IC is associated with a substantial reduction in exercise performance, deterioration of quality of life, reduced physical function and low physical activity levels, which develops morbidity and increases mortality risk (Aboyans et al., 2018).

Current clinical recommendations for first-line treatment of IC includes supervised exercise programmes aimed to improve exercise performance, leg symptoms

and quality of life (Gerhard-Herman et al., 2017). Exercise can be safely prescribed to patients with IC, with supervised exercise programmes having an exceedingly low all-cause complication rate of 1 event per 10340 hrs of patient training hours (Gommans et al., 2015), and is similarly as beneficial but more cost effective than revascularisation procedures (Reynolds et al., 2014). Exercise can improve cardio-respiratory physiology, endothelial function, mitochondrial function and strength in patients with IC enabling improved exercise performance (Harwood et al., 2016). Exercise guidelines for IC recommend interval walking as primary mode of exercise in combination with other modes of aerobic exercise and resistance exercise as an adjunct exercise (M Gerhard-Herman et al., 2017). Walking exercise to maximal or near maximal claudication pain 2 to 3 times a week for 12 to 24 weeks has a strong evidence-base to improve claudication onset distance (~128%) and peak walking distance (~82%) (Lane et al., 2017). Arm ergometry is a claudication pain free aerobic exercise mode for patients with IC which allows a greater exercise volume to be performed compared to walking which has shown to increase pain free walking and walking distance, likely through improving cardio-respiratory physiology (Tew et al., 2019). Resistance training has a valuable complementary role in supervised exercise programmes for improving muscle size and strength, contributing to improving walking performance and physical function (Parmenter et al., 2019). However, supervised exercise programmes have poor uptake and adherence, in part to patients' difficulty to tolerate high levels of pain during walking exercise and their uncertainty of the benefits of walking, which causes pain, to reduce their symptoms, therefore presenting a substantial motivational challenge for patients (Gorely et al., 2015). Additionally, time is cited as a barrier to exercise with many

patients unable to manage 2 to 3 times a week of ≥60-minute exercise sessions for prolonged periods (Gorely et al., 2015; Harwood et al., 2016). Therefore, there is a need to present alternative exercise modes for patients with IC that are effective, claudication-free and time-efficient to address the poor uptake and adherence associated with supervised exercise programmes for this population.

BFR-RE is a mode of exercise capable of inducing hypertrophy, strength and muscular endurance simultaneously (Centner et al., 2019; Counts et al., 2016; Sousa et al., 2017). The technique involves the application of an external compression around the proximal region of the exercising limb, intended to occlude venous return to elevate levels of metabolic stress whilst lifting low loads (20 - 40% 1RM; 15 – 30 repetitions per set) (Patterson et al., 2019). Muscle perturbations facilitated by BFR are thought to increase muscle fibre recruitment, and activate systemic hormone production (Manini et al., 2012), myofibrillar and mitochondrial protein synthesis (Groennebaek et al., 2018; Sieljacks et al., 2019), angiogenesis (Larkin et al., 2012) and mitochondrial biogenesis (Groennebaek & Vissing, 2017). Muscular adaptations resulting from BFR-RE are comparable to resistance exercise performed at high-load or low-load to volitional exhaustion (Centner et al., 2019; Grønfeldt et al., 2020; Sieljacks et al., 2019). Given muscular development from BFR-RE is achieved at low loads and moderate exercise volumes, the technique is potentially more tolerable and time-efficient than resistance exercise performed at high-load or low-load to volitional exhaustion. BFR-RE may be useful for clinical population when high mechanical stress and psychological challenge associated with resistance exercise performed at high load and low load to failure is contraindicated or unfeasible.

Many previous studies have shown BFR-RE to be safe and effective in varying clinical population (Cook et al., 2017; Harper et al., 2019; Hughes et al., 2019; Kambic et al., 2019; Mattar et al., 2014; Rodrigues et al., 2020). However, BFR-RE has yet to be employed in patients with IC.

Therefore, the aim of the study was to explore the safety, feasibility and preliminary efficacy of a BFR-RE programme in patients with IC. Such a study is important prior to the assessment of the clinical and cost-effectiveness of a BFR-RE programme in a large patient cohort.

6.3 Methods

Study Overview and Patients

The study is a two-arm randomised controlled trial to evaluate the safety, feasibility, and preliminary efficacy of BFR-RE in patients with IC. The study was approved by NHS and local university ethics boards (REC reference: 20/YH/0039; IRAS project ID: 260419) and was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Additionally, the study was prospectively registered at www.clinicaltrials.gov (NCT04890275).

As this was a feasibility study, no formal sample size calculation was required. The aim was a sample size of 30 patients which is suitable for a feasibility trial to provide sufficient precision of the mean and variance (Julious, 2005). Patients were recruited from the Sheffield Vascular Institute of Sheffield Teaching Hospitals NHS Foundation Trust. Eligibility criteria included (1) diagnosed PAD

with stable IC and (2) ABPI <0.9. Exclusion criteria included (1) unsuitable for or unable to exercise determined by study physician (SN), (2) ABPI >0.89, (3) symptomatic presentation of rest pain, skin ulcers or gangrene and, (4) walking is limited by a non-PAD condition or cannot walk without a walking aid. All patients provided written informed consent. Patient safety was overseen by a comprehensive research team, including a study physician (SN).

Patients were invited to Sheffield Hallam University to discuss the study in detail and were informed of the risks of participation and were given the opportunity to ask any questions prior to providing informed consent. Following consenting to participate in the study, patients' anthropometric data (stature and body mass) was collected. Baseline assessments 6MWT, ABPI, VL-MT and unilateral isometric knee extension MVT were assessed and retested after the 8-week supervised exercise programme.

Patients were randomised using block randomisation with stratification into the two resistance exercise groups performed at (1) low-load with BFR (LL-BFR) and (2) low-load (LL). Strata groups were between patients with ABPI ≥0.7 and <0.7 and between men and women.

Patients were familiarised with the exercises leg press and knee extension and were instructed on correct technique. Patients initial 1RM for leg press and knee extension was used to determine the starting exercise loads. 1RM was estimated using the repetitions to failure approach in order to minimise the risk of

musculoskeletal injury associated with 1RM testing (Cook et al., 2017; Kilgas et al., 2019).

Supervised exercise sessions were performed in the Exercise Research Laboratory (Centre of Sport and Exercise Science, Sheffield Hallam University) and took place twice a week for 8 weeks. Each session was monitored by an experienced Sport and Exercise Scientist (TP).

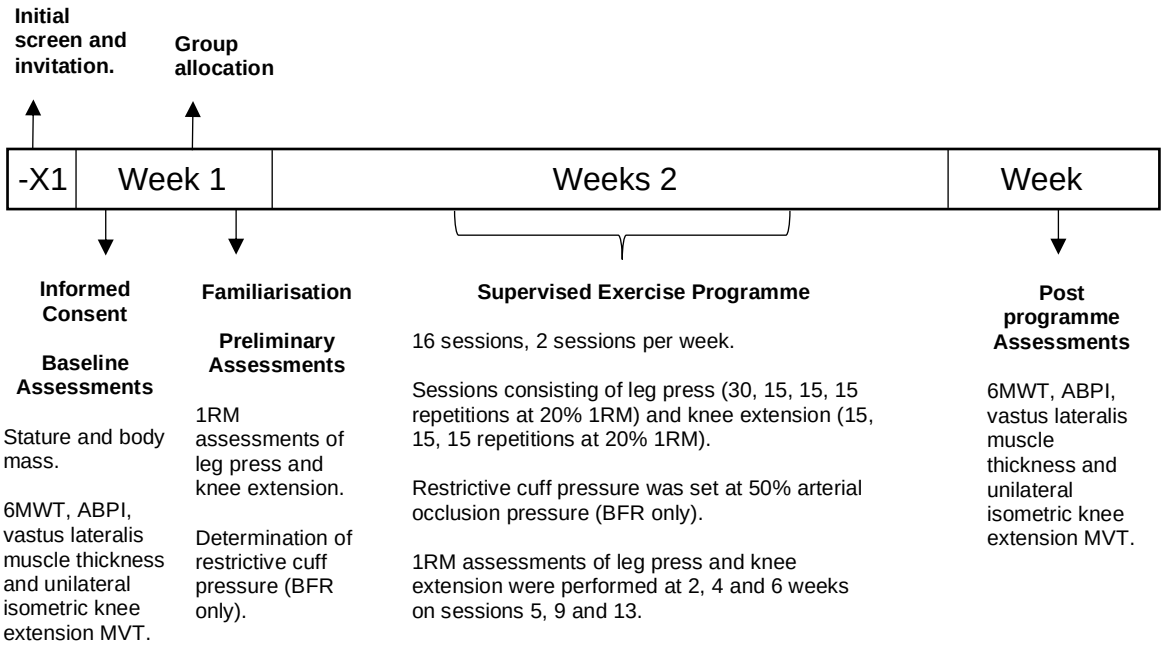


FIGURE 13: Study protocol timeline.

Determination of One repetition Maximum

1RM for leg press and knee extension was estimated using repetitions to failure approach based on previously tested protocols (Cook et al., 2017; Kilgas et al., 2019) to determine the load used during resistance exercise. Patients performed 10 repetitions at a load of low effort. The load was progressively increased until momentary failure occurred within 10 repetitions. Momentary failure was determined when, despite maximum effort, the patient was unable to complete a repetition through the full range of motion. 1RM was then predicted using the Brzycki equation (Brzycki, 1993): load ÷ (1.0278- [0.0278 × number of repetitions]). The Brzycki equation has shown excellent predictive accuracy of actual 1RM for leg press (0.96 ICC) and knee extension (0.99 ICC) (McNair et al., 2011). 1RM was determined at baseline and retested at the 2nd (5th session), 4th (9th session) and 6th week (13th session) to set the load throughout the exercise programme.

Determination of Blood Flow Restriction

Restrictive cuff pressure for LL-BFR was set relative to AOP in accordance with established methods (Laurentino et al., 2020). Patients laid in a recumbent position in a quiet unlit room for 10 min. A 13 x 85 cm nylon cuff (SC12, Hokanson, Indianapolis, USA) was applied at the most proximal portion of the thigh and 8 MHz vascular Doppler probe (HI-Dop vascular Doppler, Ana Wiz, Surrey, UK) positioned on the posterior portion of the medial malleolus on the branches of the tibial artery of the same leg. The cuff was inflated (E20 Rapid cuff inflator and AG101 Cuff Inflator Air Source, Hokanson, Indianapolis, USA) until interruption of auditory signal of arterial blood flow suggesting arterial occlusion and the final

pressure was recorded. The procedure was repeated for the opposite leg. The lowest arterial occlusion pressure of the legs was used to set the external compression. Typically, the lowest arterial occlusion pressure was in the leg most affected by PAD. If complete arterial occlusion could not be achieved by 220 mmHg in either leg, the pressure recorded was capped at 220 mmHg to minimise undue pain for the patient. The mean arterial occlusion pressure was 149.6 ± 35.4 mmHg.

Supervised Exercise Programme

Patients began with a standardised warm up consisting of 5-min light cycling followed by lower body resistance exercises leg press (Pro 2 Seated Leg Press, Life-fitness, Illinois, USA) and knee extension (SP100, TECA Fitness, Montesilvano, Italy). Both groups (LL-BFR and LL) performed 4 sets of 30, 15, 15, 15 repetitions of leg press and 3 sets of 15, 15, 15 repetitions of knee extension at 20% 1RM.

The LL-BFR group performed the resistance exercises with the addition of a restrictive cuff (13 cm wide, SC12L segmental pressure Cuff, E20 Rapid Cuff Inflator and AG101 Cuff Inflator Air Source, Hokanson, Indianapolis, USA) placed around the proximal thigh of both legs. The restrictive cuff was inflated during exercise, including the in between sets rest period, but was deflated between the rest period between the two resistance exercises. Restrictive cuff pressure was set to 50% of AOP in accordance with guidelines (Patterson et al., 2019).

Safety

Safety of the research protocol was defined by the number, type and severity of adverse events. Potential adverse events were explained to patients in detail during the informed consent process. Patients were asked to notify the research team immediately if an event occurred. Adverse events were documented, reported and assessed by the research team.

Feasibility

Recruitment rates were measured as rate of invited patients who were eligible and consenting. Attrition rates were established as dropout and discontinuation of the exercise programme. Suitability of allocation procedures were evaluated by reasons for dropout or discontinuation of exercise programme and comparing attrition rates between the two exercise groups. Adherence was monitored by exercise session attendance. Completion rates were defined as the number of patients attending the post programme assessments.

Exercise Tolerance

Patients' physiological responses to exercise were taken using heart rate (HR) and blood pressure monitoring. Patients HR was monitored was monitored when exercising using a chest strap (TICKR, Wahoo, Atlanta, USA). Patients' blood pressure was assessed immediately at the end of each exercise set using an automatic sphygmomanometer (HEM-8712, Omron Healthcare, Kyoto, Japan).

Patients' perception of exercise intensity, exercise induced pain and affective valence was assessed immediately at the end of each exercise set using RPE

(Borg, 1982), ratings of pain (Borg, 1998), and the feeling scale (Hardy & Rejeski, 1989), respectively.

Visual analogue scales (0 – 10 cm) were used 10 minutes post exercise to assess patients' perceived level of enjoyment, difficulty, fatigue, tolerance, effectiveness and safety to the exercise session. A negative response was represented at 0 cm of the scale (e.g. not at all enjoyable) and positive response was represented at 10 cm of the scale (e.g. I enjoyed it very much).

Exercise task self-efficacy was assessed using a 2-item measure were patients rated their confidence (as a percentage) in their ability to repeat the exercise session (Jung et al., 2014). Item-1 was ''how confident are you that can perform one bout of exercise a week for the next four weeks that is just like the one you completed today?''. Item 2 was ''how confident are you that can perform two bouts of exercise a week for the next four weeks that is just like the one you completed today?''

Intentions to engage in the exercise just completed over the next month was assessed using a 2-item measure (Jung et al., 2014). Patients were asked ''Please rate the extent to which you agree with the following statements 1) I intend to engage in the type of exercise I performed today once per week during the next month and 2) I intend to engage in the type of exercise I performed today twice per week during the next month''. Responses were rated on a 7-point scale with anchors ''very unlikely'' (1) to ''very likely'' (7).

Measures of exercise tolerance described above were recorded on sessions 1, 8 and 16. The mean of the measures over the 3 sessions were used for analysis.

Assessments

Six-minute walk test

The 6MWT was used to assess patients walking performance. The 6MWT is frequently used to assess walking performance in patients with IC (Mcdermott et al., 2009; Nordanstig et al., 2014) and has demonstrated excellent intraday test-retest reliability (Sandberg et al., 2019). The 6MWT was conducted following the American Thoracic Society guidelines (Enright, 2003). The 6MWT was performed indoors, in a long, flat, and straight corridor on hard flooring with the walking circuit set at 20 m in length. Patients were asked to complete as many walking circuits as possible in the 6-minute period. Patients were informed that they could rest at any point during the 6MWT. During the 6MWT, patients were given standardised phrases of verbal encouragement at each minute of the test. The total distance covered in the 6-minute period, time until onset of IC and ratings of pain (Borg, 1998) at test end were recorded and used for analysis.

Ankle-brachial pressure index

The ABPI was assessed following the gold standard Doppler ultrasound technique (Aboyans et al., 2012). The ABPI was measured for both legs and only ABPI values <0.9 were used for analysis.

Vastus lateralis muscle thickness

VL-MT was measured via B-mode ultrasonography (Sonimage MX1, Konica Minolta, Tokyo, Japan) following established standardised procedures (Ticinesi et al., 2018). Muscle thickness is easily determined with ultrasound imaging, has a high correlation with cross-sectional area of muscle (Abe et al., 1997), and is reliable (English et al., 2012; Nijholt et al., 2017). Both legs of the patient were measured. Patients were asked to lie on a hospital bed with the knee fully extended and to maintain a resting condition throughout the test. The midpoint between the greater trochanter and lateral epicondyle and the midpoint between the medial and lateral edges of the vastus lateralis provided the reference point for ultrasound imaging. A clear image of the superficial and deep aponeurosis was obtained and recorded. Images were exported and analysed using computer software (ImageJ, U.S. National Institutes of Health, Maryland, USA). Vastus lateralis muscle thickness was determined as the mean distance between the superficial aponeurosis and the deep aponeurosis at three different positions (left, middle, right) of the image (**FIGURE 14**).

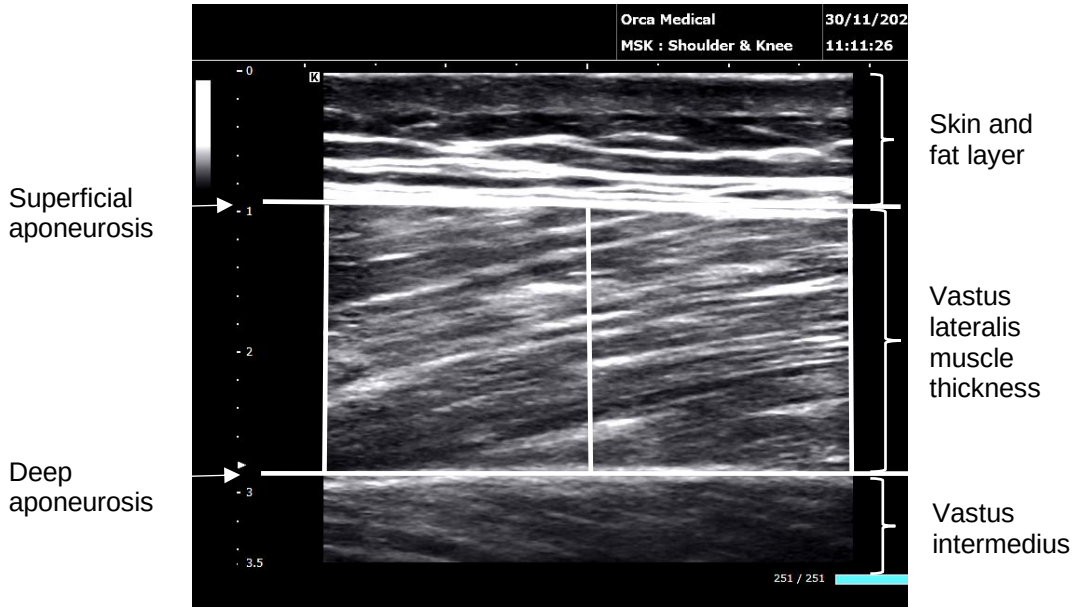


FIGURE 14: Representative recording of VL-MT at three different levels of the picture.

Maximal voluntary torque

Unilateral isometric knee extension MVT was performed using the Cybex Humac Norm Isokinetic Extremity System (Computer Sports Medicine Incorporated, Massachusetts, USA). Isokinetic dynamometry is the gold standard for measuring muscle function (Drouin et al., 2004). An isokinetic dynamometer operating in an isometric mode enables measurement of MVT in a predetermined limb position without limb movement allowing a safe maximal effort to be performed (Alvares et al., 2015). Isometric MVT is a well-established technique to assess leg strength in PAD (Mcdermott et al., 2009; Mcdermott, Criqui, et al., 2004; Scott-Okafor et al., 2001) and has shown excellent reliability (Drouin et al., 2004; van Driessche et al., 2018). Patients were seated with the knee and hip joints at 90° flexion, with the waist and thigh strapped to limit extraneous movements. First, patients performed a warm-up of 5 repetitions of 3 second

submaximal isometric knee extensions. Following this, patients were asked to perform three maximal efforts lasting 3 seconds with a minimum 60 second rest between each effort. During the determination of MVT, patients received visual feedback of the force signal and strong verbal encouragement to motivate maximal efforts. The highest peak MVT of the three efforts was used for analysis.

Statistical Analysis

Safety and feasibility of LL-BFR was assessed by number and severity of adverse events and rates of eligibility, recruitment, attrition, completion and exercise adherence were used to assess.

Given this is a feasibility study, no formal sample calculation was required. Thirty patients were recruited as this is sufficient to provide precise estimates of feasibility outcomes and not cause undue burden on patients (Lancaster et al., 2004).

All data is presented as means ± standard deviations unless stated otherwise. As this study was not powered to detect statistical differences in outcomes (e.g., p-value < 0.05), estimated mean differences are presented with 95% confidence intervals. Statistical analysis was conducted using SPSS (Version 26, Chicago, United States).

6.4 Results

Recruitment and Patients

Recruitment took place between April 2021 and April 2022. Of 167 patients screened, 79 met the inclusion criteria and 30 were recruited (**FIGURE 15**). Eligibility and recruitment rates were 47% and 38%, respectively. Patients were randomised to exercise groups (LL-BFR: n = 15, LL: n = 15). Patients' characteristics were similar between the two groups at baseline (**TABLE 14**).

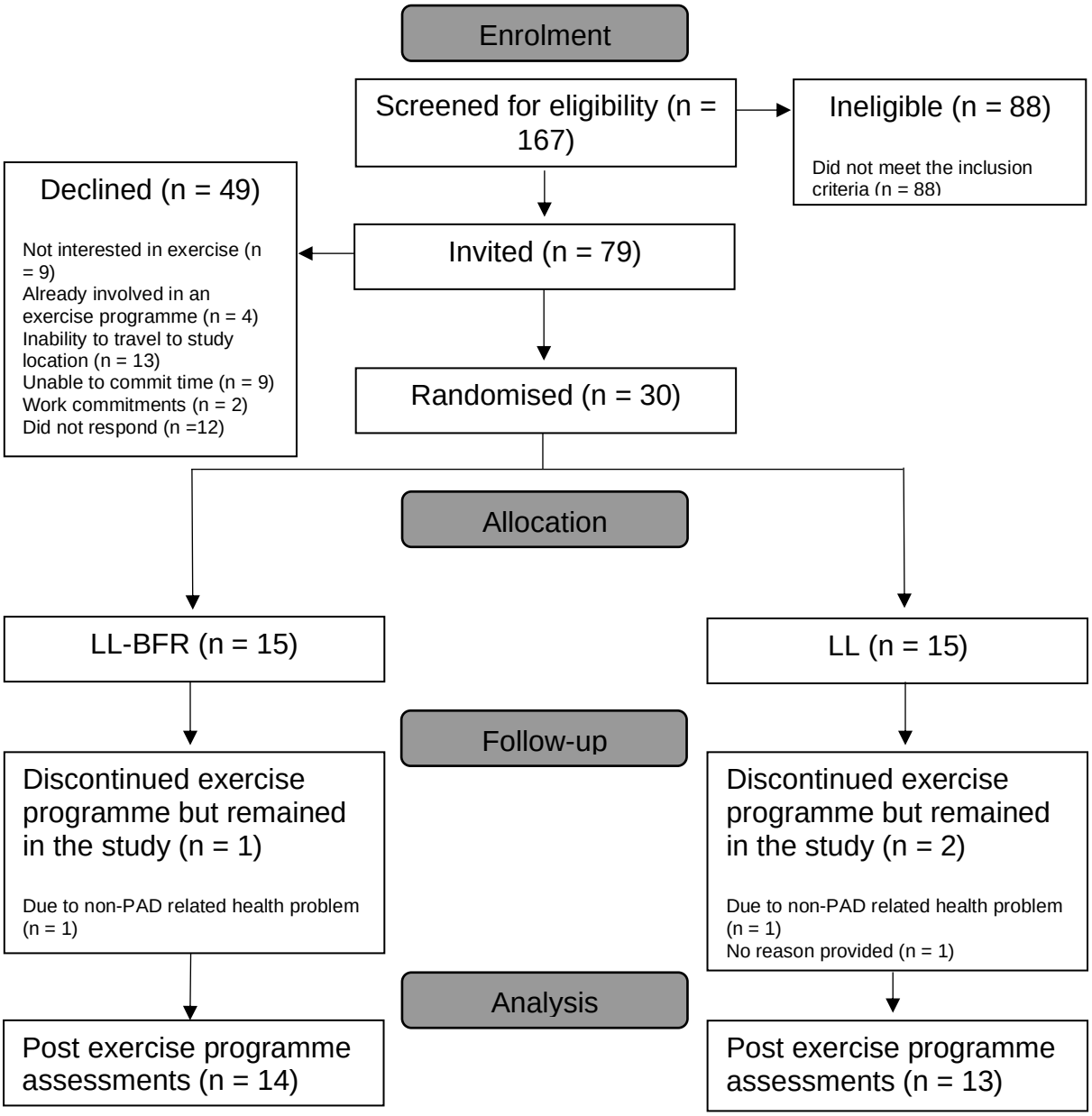


FIGURE 15: CONSORT **f**low diagram.

TABLE 14: Patients' baseline characteristics.

	LL-BFR (n = 15)	LL (n = 15)	Total (n = 30)
Age (years)	66.8 ± 8.6	71.6 ± 9.1	69.0 ± 9.0
Sex, Female	3 (20%)	3 (20%)	6 (20%)
Ethnicity (%white)	100	100	100
Stature (cm)	168.6 ± 11.7	171.1 ± 10.2	169.8 ± 10.9
Body Mass (kg)	79.4 ± 12.3	77.6 ± 12.1	78.6 ± 12.0
BMI ($kg \cdot m^2$)	27.9 ± 3.1	26.5 ± 3.5	27.3 ± 3.3
Bilateral Claudication	7 (47%)	5 (33%)	12 (40%)
ABPI	0.62 ± 0.16	0.69 ± 0.11	0.65 ± 0.14
Current Smoker	4 (27%)	3 (20%)	7 (23%)
Previous Smoker	14 (93%)	11 (73%)	25 (83%)

Safety

No adverse events or serious adverse events were recorded during the study period.

Attrition, Adherence and Completion

All 30 patients were retained in the study. Three patients discontinued participation in the exercise programme at some point during the study period for reasons unrelated to the study but remained in the study (LL-BFR: n = 1, LL: n = 2). Adherence to the exercise programmes was 81% in total (LL-BFR = 78%, LL = 84%). Completion rates was 90% in total (LL-BFR = 93%, LL = 87%).

Exercise Tolerance

Overall changes in 1RM from baseline to week 6 were as follows (mean difference and 95% CI): leg press 63.6 kg [36.9, 90.3] and knee extension 21.9 kg [13.3, 30.4] (**FIGURE 16**).

Peak HR was 101 ± 12 $b \cdot min^{-1}$ for LL-BFR and 94 ± 27 for LL. Peak systolic and diastolic blood pressure was 180 ± 27 mmHg and 100 ± 14 mmHg for LL-BFR and 170 ± 34 mmHg and 93 ± 16 mmHg for LL.

Peak RPE was 14.1 ± 1.8 (“somewhat hard” to “hard”) for LL-BFR and 12.9 ± 1.7 (“somewhat hard”) for LL. Peak pain was 4.2 ± 2.0 (“moderate” to “strong”) for LL-BFR and 3.4 ± 1.6 (“moderate”) for LL. Average feeling scale was 3.5 ± 1.9 (“good”) for LL-BFR and 3.9 ± 1.0 (“good’’) for LL.

Outcomes of visual analogue scales (0 – 10 cm) were rated positively for both LL-BFR and LL: Enjoyment; LL-BFR = 8.9 ± 1.2, LL = 9.4 ± 0.6, Difficulty; LL-BFR = 3.7 ± 2.3, LL = 3.9 ± 3.0, Fatigue; LL-BFR = 2.3 ± 2.0, LL = 3.3 ± 3.0, tolerance; LL-BFR = 7.9 ± 1.8, LL = 8.3 ± 1.5, Effectiveness; LL-BFR = 8.7 ± 0.8, LL = 8.9 ± 0.7, and Safety; LL-BFR = 9.7 ± 0.3, LL = 9.8 ± 0.2.

Patients’ confidence to complete the exercise session twice per week was 94% out of 100% for LL-BFR and 98% out of 100% for LL.

The mean values for intention to engage in type of exercise twice per week was 6.9 ± 0.4 (“likely”) for LL-BFR and 6.6 ± 0.9 (“likely”) for LL.

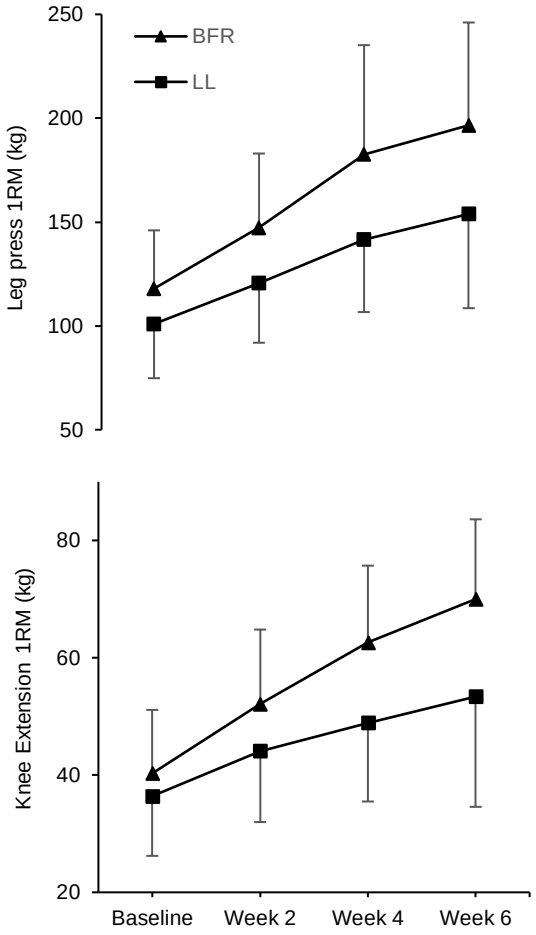


FIGURE 16: Assessments of 1RM for leg press and knee extension used to prescribe exercise load throughout the exercise programme. Displayed as means and 95% CI.

Assessments

Data from assessments are reported in **TABLE 15**. 6MWT distance was increased from PRE to POST by 55.2 m [42.4, 67.9] for LL-BFR and 47.5 m [15.2, 79.7] for LL. However, 86% of patients in LL-BFR improved 6MWT distance by >35.5 m (which represents a large clinically important difference) from PRE to POST compared with 46% of patients in LL. In the 6MWT, time to claudication

pain was increased 44.7 s [20.8, 68.6] for LL-BFR but was not for LL (4.4 s [-32.4, 23.6]), and pain at end of 6MWT may have been reduced 1.1 CR-10^{+} [-0.1, 2.4] following LL-BFR but not for LL (-0.2 CR-10^{+} [-1.2, 0.8]). ABPI, vastus lateralis muscle thickness and MVT displayed similar results between PRE and POST for LL-BFR and LL.

TABLE 15: A battery of assessments were performed PRE and POST exercise programme to assess changes in 6MWT, ABPI, vastus lateralis muscle thickness and unilateral isometric knee extension MVT.

Variable	**PRE**	**POST**	**% Difference**
6MWT			
Distance (m)			
LL-BFR	371.3 ± 91.9	426.5 ± 102.2	15%
LL	352.8 ± 117.7	400.3 ± 105.4	13%
Time to claudication (s)			
LL-BFR	127.5 ± 68.5	172.2 ± 59.8	35%
LL	105.9 ± 67.9	110.3 ± 52.5	4%
Pain (CR-10^{+})			
LL-BFR	4.3 ± 2.6	3.1 ± 1.8	-28%
LL	4.1 ± 1.5	4.3 ± 2.2	5%
ABPI			
LL-BFR	0.64 ± 0.15	0.67 ± 0.21	5%
LL	0.74 ± 0.11	0.72 ± 0.14	-3%
Muscle Thickness (mm)			
LL-BFR	21.9 ± 2.7	21.8 ± 3.3	0%
LL	21.7 ± 4.1	22.1 ± 4.2	2%
MVT (N·m)			
LL-BFR	126.3 ± 37.1	123.5 ± 38.3	-2%
LL	105.3 ± 50.1	102.5 ± 47.2	-3%

6.5 Discussion

This study explored the safety, feasibility and preliminary efficacy of an 8-week exercise programme of lower-body low-load resistance exercise with BFR in patients with IC. Our findings indicate the study procedures were safe and feasible, and LL-BFR may potentially improve walking performance in patients with IC.

The most important aspect of the study was to determine the safety of BFR-RE in patients with IC. The risks of using BFR-RE in PAD has been an area of uncertainty, and previous studies have cited PAD as a possible contraindication to BFR-RE (Brandner et al., 2018; Patterson & Brandner, 2018; Spranger et al., 2015). A primary concern is an exacerbated metaboreflex activation from BFR-RE leading to elevated hemodynamic responses during exercise that could precipitate adverse cardiovascular or cerebrovascular events in cardiac and vascular disease patients (Spranger et al., 2015). Our data implies a heightened cardiovascular response to LL-BFR compared to LL, which is consistent with previous studies observing an increase in HR, systolic and diastolic blood pressure, and mean arterial pressure with BFR-RE in healthy young (Poton & Polito, 2016) and older adults (Scott et al., 2018), hypertensive women (Pinto et al., 2018a) and coronary artery disease patients (Kambič et al., 2021). Importantly, the observed increases in HR and blood pressure are consistently <120 $b \cdot min^{-1}$ and <210/110 mmHg and within the normal range expected during exercise (Fletcher et al., 2001). Importantly, to date no adverse events have occurred in high-risk patient groups following BFR-RE (Kambic et al., 2019; Madarame et al., 2013; Pinto et al., 2018).

Determining the restrictive cuff pressure is critical in providing a safe and effective stimulus from BFR-RE. The beneficial adaptations of BFR-RE in muscle is determined by the restrictive cuff pressure that balances the level of muscle activation and fatigue (contractile/metabolic impairment). It is important that the restrictive cuff provides sufficient pressure to provide a training stimulus. Low restrictive cuff pressures (≤30% arterial occlusion pressure) are unlikely to augment a muscular/metabolic response sufficient to produce a worthwhile training stimulus due to not effectively restricting venous blood to cause blood pooling when exercising. As such, little research exists applying low pressures. Increasing the restrictive cuff pressure in turn increases the neuromuscular and metabolic response to BFR-RE (Fatela et al., 2016). However, a consequence to this is a reduced exercise volume and increased cardiovascular demand, RPE and pain. High restrictive cuff pressures (≥80% AOP) and complete arterial occlusion (≥100% AOP) may increase the risk of adverse cardiovascular events, although these outcomes are rare (Nakajima et al., 2006; Patterson & Brandner, 2018; Spranger et al., 2015). Additionally, such pressures can limit the tolerable duration of exercise and result in a decrement in muscular response (Cook et al., 2007; Yasuda et al., 2008), compromising the effectiveness of BFR-RE as achieving a high exercise volume appears crucial in potential mediating factor for skeletal muscle hypertrophy (Burd et al., 2010) and vascular remodelling (Prior et al., 2003). It appears the restrictive cuff pressure has a broad window of effectiveness that occurs at moderate pressures (40% - 80% AOP). Such pressures facilitate an increase in muscle activation and development of peripheral fatigue, also allowing sufficient exercise volumes to be performed and

appear safe (Cook et al., 2007; Evans et al., 2010; Fahs et al., 2014; Karabulut et al., 2010; Kim et al., 2009; Patterson & Ferguson, 2010; Suga et al., 2010; Takada et al., 2012).

Among the challenges experienced in the trial was patient recruitment. However, recruitment was considered a success given the target sample (n = 30) was achieved within the trial timeframe despite the COVID-19 pandemic imposing substantial pressure on clinical services. Nevertheless, recruitment rates at 38% is low in comparison to previous studies and is an area for improvement for a fully powered randomised control trial (Harwood et al., 2016). A key component of the Framework for Developing Complex Interventions stipulated by the Medical Research council is the engagement of stakeholders (Skivington et al., 2021). Patients are key stakeholders and meaningful engagement with patients in research design was needed to maximise the potential of developing or identifying an intervention that wanted. This aspect of research design was missing in this Experimental Chapter and may have affected the recruitment. Additionally, qualitative analysis revealed many patients are uncertain of the benefits of exercise and therefore may be less willing to commit their time to it (Harwood et al., 2017). Structure education is warranted in IC patients (Gorely et al., 2015), therefore a possible strategy could be to offer education workshops focused on exercise promotion alongside the exercise intervention to promote recruitment.

From eligible patients that were invited to partake in the study but declined, 27% of the responses were due to the inability to travel to the study location. It is

acknowledged of the difficulty for patients to travel to central exercise locations which requires strong motivation to continue study participation (Harwood et al., 2017). A crucial feature to improve uptake for a future, fully powered, randomised controlled trial would be to offer the exercise programme across several accessible sites and times to improve availability for patients and reduce travel burden.

The high adherence rates for the LL-BFR group are an encouraging sign of the acceptability of this exercise programme aimed at patients with IC. To support this, visual analogue scales were rated positively for perceived enjoyment, tolerance and difficulty following LL-BFR and intentions to engage in future sessions was high. This demonstrates the high interest and self-motivation from our patients, which will be a decisive factor for the success of a definitive trial and any wider roll-out of the exercise programme. The strength in the delivery of the exercise programme and baseline assessments contributed to the high adherence rates observed. A single Sport and Exercise Scientist delivered all the sessions for the patient which offered one-to-one engagement, familiarity, and rapport building. Such factors contribute to enjoyment, affect and adherence to exercise (Raedeke, 2007) as a result dropouts to the exercise programme were minimal. Additionally, exercise programmes that incorporate behaviour change techniques such as self-monitoring, reinforcement, goal setting and feedback are effective in enhancing adherence (Room et al., 2017). Although not intended, the repeated 1RM assessments in the exercise programme gave the patients an opportunity to monitor their progress through the trial. Observing an improvement

in 1RM assessment was motivating to the patient and may have contributed to the high adherence rates and is an important consideration for future trials.

A high completion rate was observed for the LL-BFR (93%), evidence of patients' commitment to complete the trial and interest to observe any changes in the post exercise programme assessments. Although not formally explored in the trial, many patients in LL-BFR described feelings of pain relief following the LL-BFR sessions and reported a perception of improved walking for normal daily activities through delayed onset of IC or greater tolerance to IC after approximately 8 BFR sessions (4 weeks into the exercise programme). Such beliefs may have contributed to the patients' positive intentions to engage in future sessions and commitment to complete the trial to formally address whether walking performance had improved.

The outcomes of the 6MWT in the present study hold potential for explaining in a fully powered randomised trial, the extent which BFR-RE could affect walking performance in patients with IC. Though the data should not be over-interpreted, it is encouraging that 6MWT distance increased by 15% and time to claudication pain was increased by 35% following 8-weeks of LL-BFR and 86% of patients in the LL-BFR group improved 6MWT distance by >35.5 m which represents a large clinically important difference (Gardner et al., 2018). LL-BFR may be more beneficial than moderate to high load resistance exercise which report modest (8%, p <0.08) improvements in 6MWT after 12 to 24 weeks (Parmenter et al., 2019). Instead, improvements in 6MWT following LL-BFR are more comparable to seen following 12 to 24 weeks of walking exercise which report 11% – 14%

increase in 6MWT distance following 12 to 24 weeks (Gardner et al., 2002; Szymczak et al., 2016).

Likely mechanisms that contribute to an increased exercise performance in IC include changes in cardio-respiratory physiology, endothelial function, mitochondrial number and activity and muscle conditioning (Harwood, Cayton, et al., 2016). BFR elicits adaptive signals through reduced muscle oxygenation, enhanced shear stress and increased markers of oxidative stress during exercise which activates systemic hormone production (Manini et al., 2012), myofibrillar and mitochondrial protein synthesis (Groennebaek et al., 2018; Sieljacks, Wang, et al., 2019), and angiogenesis (Larkin et al., 2012). Prolonged BFR exposure improves exercise performance likely due to increased muscle function and improved oxygen delivery/extraction by the working muscles (Fahs et al., 2015; Ferguson et al., 2018; Lundby et al., 2009), and may have contributed to an improved walking performance in patients with IC.

Improved walking performance and increased time to claudication time may have occurred through the analgesic effect of BFR-RE. BFR-RE has shown to reduce pain across a training programme in a range of clinical conditions (Ferraz et al., 2018; Hughes et al., 2019). BFR-RE has shown to improve pain reduction and physical function to a greater extent than traditional high-load resistance exercise in rheumatoid arthritis (Rodrigues et al., 2020) and following surgery for ligament repair (Hughes et al., 2019). Therefore, it may be possible that BFR-RE has a dual effect in PAD, inducing adaptations and reducing pain that could enable improved exercise performance. The potential analgesic effect of BFR-RE in PAD

is an important consideration for the development of future exercise practices. If BFR-RE is effective in reducing pain and increasing exercise tolerance in PAD, it could be implemented in combination with aerobic exercise, such as walking. This would aim to facilitate cardiorespiratory adaptions that are important to the improvement in exercise performance in PAD to optimise the exercise programme (Harwood et al., 2016) and boost patients' confidence in walking which may increase their activities of daily living and QoL.

Interestingly, no changes were observed for vastus lateralis muscle thickness and MVT. This was unexpected given studies frequently demonstrate an increase in muscle size and strength following BFR-RE which use loads of 20% to 30% 1RM (Centner et al., 2019). The decision to use loads of 20% 1RM for LL-BFR was to encourage a greater amount of exercise volume to be performed in order to facilitate endurance type adaptations. To observe changes in these outcomes a higher load (~30% 1RM) or high restrictive cuff pressure (80% AOP) may be required. A study investigating the effects of different resistance exercise protocols found an augmented hypertrophy response from resistance exercise at 20% 1RM from an increase in restrictive cuff pressure from 40% to 80% AOP but not at exercise loads of 40% 1RM (Lixandrão et al., 2015). In the same study, it was demonstrated that strength response did not alter despite modulation in restrictive cuff pressure or exercise intensity. To provide a more mechanistic insight to the effect of BFR on exercise performance in patients with IC a larger set of outcomes which considers hemodynamics (e.g blood flow and flow mediated dilatation), blood analysis (e.g mitochondrial number and function), muscle architecture (e.g. pennation angle and fascicle length), and muscle

function (e.g. rate of force development and rates of fatigue) should be considered.

This study has presented a novel exercise mode as a potential alternative to walk exercise for patients with IC to address the poor uptake and compliance associated with walk exercise programmes. A limitation of the study was an exclusion of a walk exercise group. This would enable the comparison of uptake, adherence, safety and effectiveness between BFR and walk exercise. Though the decision not to include a walk exercise group was because it was considered important to first discover whether BFR provides an additional benefit to low load resistance exercise in patients with IC as a proof of concept prior to comparisons between other modes of exercise. Another limitation of the study was the patient sample. Eighty percent of the sample were men although prevalence rates of PAD are similar between men and women (Fowkes et al., 2013) and all patients were of white ethnicity, despite other ethnic groups being as vulnerable to PAD (Vitalis et al., 2013). Small sample sizes of feasibility trials increase the risk of selection bias. A future full-scale study must obtain a sample that is representative of the PAD population for generalisability of findings.

Our findings support the safety and feasibility of a BFR programme in patients with IC, observing no adverse events, good recruitment rates, high adherence and completion rates, low attrition rates, and high enjoyment levels and intentions for future exercise engagement. In addition, the findings of the present study suggest a BFR programme has the potential to improve walking performance in

patients with IC, which deserves confirmation in a fully powered randomised controlled trial.

7 General Discussion

The main aims of this research programme were to; (1) explore the perceptual, affective and physiological responses to BF-RE, (2) investigate the utility of a physical function test battery to assess the effects of exercise programmes and, (3) evaluate the safety, feasibility and preliminary efficacy of an 8-week BFR-RE programme for patients with PAD suffering IC.

Chapter Four demonstrated low-load resistance exercise in combination with BFR elevates pain whilst exercising to a greater degree than low-load and moderate-load resistance exercise without BFR, but not to the extent that negatively effects the affective response post exercise. Also, the addition of BFR to low-load resistance exercise augments the physiological response whilst exercising to a similar degree to moderate-load resistance exercise without BFR. The study also highlighted a greater perceptual and physiological response during single-joint resistance exercise compared to multi-joint exercise when matched for load (%1RM) and volume (4 sets of total 75 repetitions), which may be exaggerated by BFR.

The findings in Chapter Five indicated excellent test-retest reliability of a test battery to assess physical function in PAD patients comprising muscle thickness of the vastus lateralis, ABPI, unilateral isometric knee extension MVT and 6MWT. In addition, the smallest magnitude of change required to be interpreted as a likely beneficial change (76% chance) was of 1.5 mm for MT, 0.08 for ABPI, 17 N·m for MVC and 35.5 m for 6MWT.

Chapter Six found an 8-week exercise programme consisting of lower-body low-load resistance exercise in combination with BFR was safe, feasible and efficacious in PAD patients suffering with intermittent claudication.

7.1 Acute Perceptual, Affective and Physiological Responses to Lower-Body Low-Load Resistance Exercise with Blood Flow Restriction

Chapter Four sought to describe the acute perceptual, affective and physiological responses to different lower-body resistance exercises when performed at low-load with BFR in relation to low-load, and moderate-load without BFR. Fifteen young and twenty older adults without any known conditions or disorders participated in this randomised controlled, repeated measures design study. The purpose of this investigation in relation to the research programme was to better understand the tolerability of lower-body low-load resistance exercise with BFR prior to its utility with IC patients (Chapter Six).

BFR-RE induces hypertrophy, strength and muscular endurance (Fahs et al., 2015; Kacin & Strazar, 2011; Laurentino et al., 2012)**.** It is well known the addition of BFR to any mode of exercise causes RPE, ratings of pain, HR and blood pressure responses to increase (Brandner et al., 2018)**.** The extent of this is largely dependent on the degree of restrictive pressure of BFR applied and the exercise volume-load (Loenneke et al., 2015; Singer et al., 2020; Soligon et al., 2018)**.** Several studies demonstrate BFR-RE performed at moderate restrictive pressure (50% AOP) and not to failure produce similar or lower RPE, ratings of pain, HR and blood pressure responses to HL-RE (Freitas et al., 2019; Miller et al., 2020; Soligon et al., 2018)**.** To the authors knowledge, no study prior to this

research has compared the perceptual, affective and physiological responses to different lower-body resistance exercise performed at low-load with BFR (LL-BFR) and moderate-load ML in young and older adults. Such investigations contribute to the existing literature regarding the tolerability of BFR-RE and were warranted prior to its use in IC patients.

Several novel findings resulted from this Experimental Chapter. For instance, greater levels of pain incurred from LL-BFR compared to ML which was consistent for each resistance exercise for both young and older adults. The addition of BFR to exercise facilitates the development of peripheral fatigue which results into increased perception of pain (Husmann et al., 2018). Unfortunately, pain experienced is unwanted but a necessary to create a stimulus which muscular adaptations can result. For example, the addition of BFR to exercise lowers affect and task motivation in young males during exercise (Mok et al., 2020; Suga et al., 2021). Importantly, these perceptual and affective responses are transient and do not incur detriments to affect, fatigue or tranquillity following end of exercise as evidenced in Chapter Four and in previous studies (Mok et al., 2020; Suga et al., 2021). The increased pain with LL-BFR may be a barrier to exercise participation for some individuals (Ekkekakis et al., 2011; Fisher et al., 2017; Kim et al., 2017), though it is encouraging there are no lasting detriment to affect, fatigue or tranquillity following from LL-BFR. Nevertheless, LL-BFR may not be suitable for individuals who display low tolerance to pain and poor motivation. However, given patients with IC tend to be motivated to exercise in order to improve their leg symptoms, and the LL-BFR protocol used in the study

resulted in sub-maximal pain, lower-body low-load resistance exercise with BFR may be feasible for IC patients.

Changes in perceptual parameters induced by resistance exercise can be associated with physiological responses (Hampson et al., 2001). There are existing concerns BFR exercise increases the exercise pressor reflex resulting in an enhanced autonomic cardiovascular response that could lead to cardiovascular complications in high-risk clinical populations such as PAD (Spranger et al., 2015). However, HR and blood pressure responses are no greater with LL-BFR than ML during lower-body resistance exercise which supports evidence of its acceptable hemodynamic demand (Brandner et al., 2018). Given muscular development derived from resistance exercise is considered comparable between LL-BFR and HL (Centner et al., 2019) but HR and blood pressure responses are comparable to ML, promotes its value as an alternative to traditional resistance exercise.

Another novel finding was the type of lower-body resistance exercise (multi-joint or single-joint) influenced the perceptual and physiological response. Chapter Four reports an elevated RPE, pain, HR and blood pressure response to knee extension (single-joint) compared to leg press (multi-joint) which could be exaggerated by the addition of BFR. This is an important consideration when managing the projected perceptual and physiological stress from an exercise programme. While guidelines for safe and effective BFR practice exist (Patterson et al., 2019a), it is known the restrictive cuff pressure (Singer et al., 2020; Soligon et al., 2018), cuff width (Rossow et al., 2012; Spitz et al., 2021), type of cuff (Miller

et al., 2020) and exercise load (Loenneke et al., 2015) can have marked implications onto the perceptual or physiological response. The finding from Chapter Four demonstrates the type of resistance exercise should also be careful considered in the exercise programme design when managing the expected perceptual and physiological stress that will occur from resistance exercise prescription. As a result from this finding, the volume prescribed during knee extension for the exercise programme for IC patients (Chapter Six) was reduced to 3 sets and a total of 45 repetitions. This was in attempt to lower peak pain and improve the likelihood of completing all prescribed repetitions to minimise any detriment to exercise self-efficacy with the objective to improve exercise compliance.

These findings contribute to the existing knowledge regarding the acute perceptual, affective and physiological responses to low-load resistance exercise with BFR. However, we acknowledge that patients involved in this study were all physically active, interested in exercise and without any known conditions or disorders. Therefore, findings cannot be generalised to patients with IC. While the findings from this study can inform the design of the exercise programme for IC patients, the hemodynamic disorder associated with the disease could influence the acute perceptual, affective and physiological responses they experience.

7.2 Reliability of Test Battery to Assess Physical Function in Patients with Intermittent Claudication

Chapter Five observed excellent overall reliability for ABPI, 6MWT, MVT and VL-MT supporting the utility of the physical function test battery to assess the effects of exercise programmes in patients with IC. Such wide range of reliability statistics were reported to help practitioners interpret the data according to their preferred method. Excellent reliability has been previously observed for ABPI, 6MWT, MVT and VL-MT in a non-PAD population (Bohannon et al., 2014; Casey et al., 2019; Nijholt et al., 2017; van Driessche et al., 2018), suggesting the presence of PAD may not be detrimental to the day-to-day variation associated with the tests. However, this should be formally investigated particularly for tests MVT and VL-MT which reliability has not been previously investigated in patients with PAD. Given PAD impairs muscle function and reduces muscle quality it is possible this could increase error associated with MVT and VL-MT assessments. If this variation did exist, patients which have PAD in only one leg should have their test scores interpreted differently to the non-PAD leg when undertaking MVT and VL-MT assessments. Despite excellent overall reliability, the 6MWT and MVT was subject to systematic bias suggesting a learning effect. This is not uncommon in performance assessments and to reduce bias practitioners should include provide familiarisation to the assessments prior to actual assessments.

In order to be confident in interpreting actual changes in assessments, exercise practitioners must relate their results to the smallest worthwhile change. Many studies in the literature provide minimal detectable change for clinical tests, which is defined as the minimal change that falls outside the measurement error in the

score of an instrument used to measure a symptom (Kovacs et al., 2008). This is used to interpret the clinical relevance of results in studies on the effectiveness of treatments. If a change is greater than the minimal detectable change then there would be a ≥95% chance that it is an actual change. However, in some cases a practitioner would have to observe a >12% improvement in test scores to be confident it was an actual change (Sandberg et al., 2019). An issue with the minimal detectable change is the stringent parameters does not allow any interpretation of values that fall below it, which can make it difficult for practitioners to monitor patients progress during an exercise programme.

In Chapter Six, using the approach of Hopkins (2004) allowed the interpretation of change without stringent parameters. The findings in Chapter Six provided the minimum magnitude of change required to be interpreted as a likely change (76% chance) and it also presented a range of changes and their associated likelihoods of change to support and inform practitioners' interpretation of assessments. Such data is useful for exercise practitioners as it can provide confidence in their exercise prescription, particularly if they are trying novel exercise modes or short (<12 weeks) exercise programmes, like that presented in Chapter Seven.

7.3 Safety, Feasibility and Preliminary Efficacy of BFR Resistance Exercise for Patients with Intermittent Claudication

The overarching aim of the current thesis was to evaluate the safety, feasibility and preliminary efficacy of low-load resistance exercise with BFR in patients with IC. Chapter Four informed the BFR exercise protocol which would be employed for patients with IC. Chapter Five presented the reliability of the physical function

test battery which enabled the interpretation of changes in assessments to evaluate the efficacy of the 8-week resistance exercise programme. In Chapter Six, thirty patients with stable IC undertook an 8-week programme of lower-body resistance exercise and were randomly assigned to perform the programme at low-load with blood flow restriction (LL-BFR; *n* =15) or at low-load (LL; *n* =15). The purpose of this investigation was to explore an alternative training approach to improve exercise performance for patients with IC to address the poor uptake and compliance associated with current recommended exercise programmes.

The LL-BFR group reported high completion rates (93%), high exercise adherence (78%) and low attrition rates (0%). Importantly, the LL-BFR exercise protocols employed in the study appear safe in this population with no adverse events recorded. HR and blood pressure during exercise did not exceed 120 $b \cdot min^{-1}$ and 210/110 mmHg, which is within the normal expected range (Fletcher et al., 2001). Moreover, the LL-BFR protocol was well tolerated by patients. During LL-BFR, peak ratings for RPE was “somewhat hard” to “hard” and pain was “moderate” to “strong”. Importantly, these peak values are well below maximal ratings and comparable to that associated with moderate load resistance exercise in older adults as evidenced in Chapter Four. Affective valence was ‘’good’’ and patients rated highly for enjoyment and intentions for future engagement to this type of exercise. These findings demonstrate that lower-body resistance exercise performed at low-load with BFR is safe and feasible for patients with IC.

In Chapter Five, LL-BFR appears to have a positive effect on walking performance in patients with IC. After 8-weeks of two exercise sessions a week (total of 16 exercise sessions), the LL-BFR group 6MWT distance increased by 15% and time to claudication pain was increased by 35%. At an individual level, clinical improvement in 6MWT distance (an increase by >35 m) was achieved in 86% of patients in LL-BFR.

In comparison to studies employing traditional resistance exercise, Szymczak et al., (2016) reported modest improved in 6MWT distance (8%, p = 0.07) following 12 weeks of three times a week resistance exercise. Sessions involved of 4 exercises that targeted the lower-extremity musculature, performing 3 sets of 15 repetitions, load was not specified. Additionally, Mcdermott et al., (2009) found 24 weeks of three times a week resistance exercise had no effect on 6MWT distance (-1%, p =0.24). Sessions involved 3 exercises that targeted the lower-extremity musculature, performing 3 sets of 8 repetitions at ~80%1RM, with an additional 2 exercises performed at bodyweight. The conflicting outcomes between studies may be attributed by the different exercise protocols used, with exercise performed at higher volumes appearing to improve 6MWT distance. As such, the high exercise volumes associated with BFR-RE may be the catalyst for improved walking performance in IC.

The improvements in 6MWT following LL-BFR may be more comparable to that seen following walking exercise. Szymczak et al., (2016) reported an improvement of 14% % (p = 0.004) after 12 weeks of 3 times a week, and Gardner et al., (2002), and Gardner et al., (2002) reported an improvement of

11% (p = 0.042) after 24 weeks 3 times a week. Interestingly, the improvements observed following walk training involved substantially more sessions than LL-BFR (LL-BFR = 16 sessions, walking ≥36 sessions).

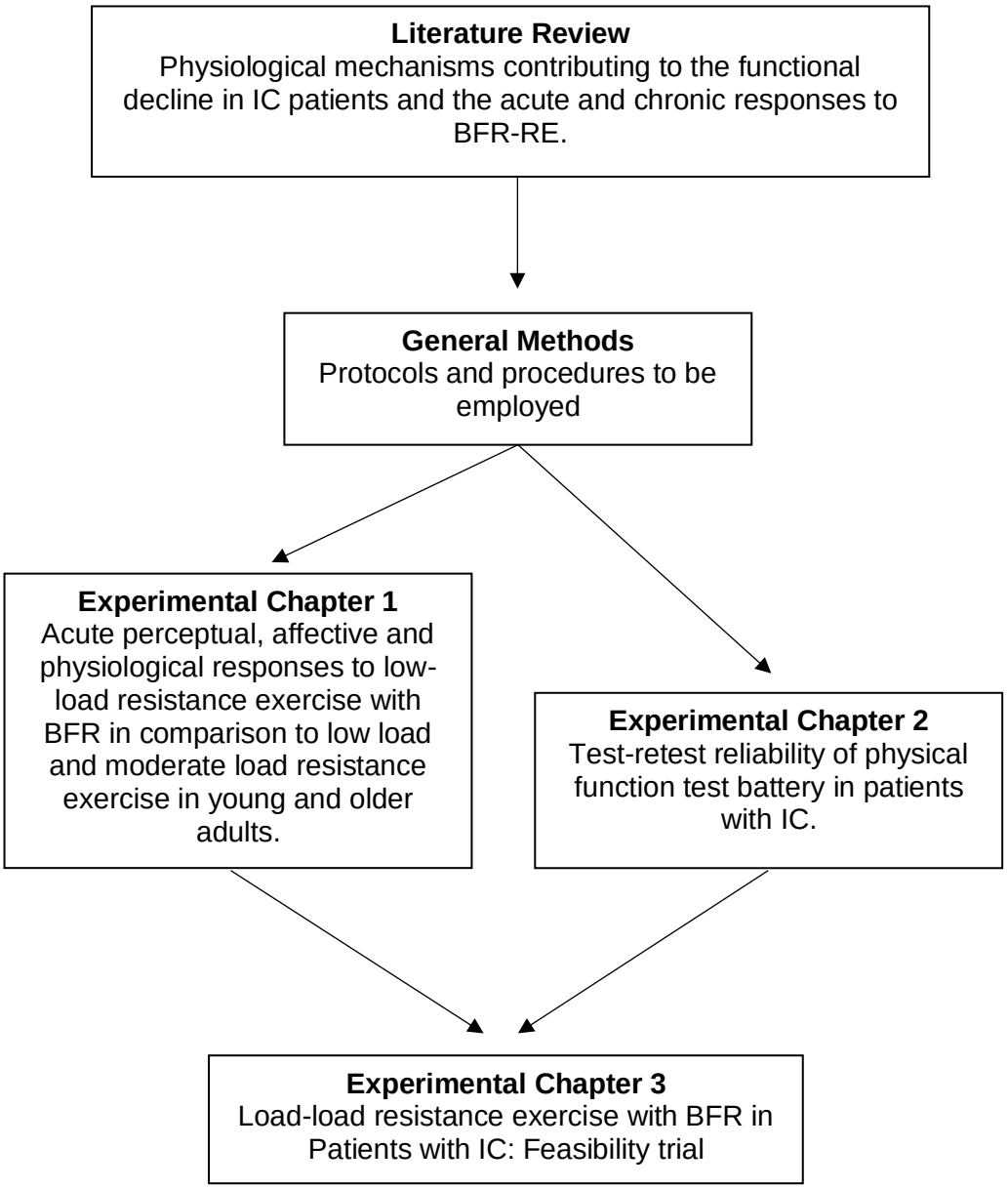
Further research is required to elucidate the mechanisms which BFR-RE improves exercise performance in PAD. BFR-RE showed to increase strength assessed via 1RM of leg press and knee extension though this did not transfer to improved isometric knee extension MVC, and it did not show to increase vastus lateralis size or ABPI. Future research should consider changes in hemodynamics (e.g blood flow and flow mediated dilatation), blood analysis (e.g mitochondrial number and function), muscle architecture (e.g. pennation angle and fascicle length), and muscle function (e.g. rate of force development and rates of fatigue) following BFR-RE to provide a more mechanistic insight to the effect of BFR-RE on exercise performance in PAD. Additionally, future research should consider the analgesic effect of BFR-RE in PAD and its influence on walking performance. An improved tolerance to pain and exercise performance has large implications in the QoL of PAD patients (Izquierdo-Porrera et al., 2005; Nordanstig et al., 2014). Furthermore, studies may wish to take advantage of this potential analgesic effect and combine BFR-RE with aerobic exercise which is associated with high ratings of pain in PAD to further optimise exercise programmes.

Our findings suggest BFR-RE can be safely performed by patients with IC and has potential to be an effective mode of exercise to improve exercise performance. BFR-RE could become a viable alternative to walk training for

patients with IC which could prove more time-efficient or be used in combination with walking exercise to optimise the training programme. The findings in this thesis support the safety, feasibility and efficacy of BFR-RE in patients with IC. Protocols and procedures used in Chapter Six should now inform the design of a future, fully powered randomised control trial to investigate the clinical and cost effectiveness of BFR-RE in patients with IC.

7.4 Strengths

The main strength of this thesis is the programme design where the theoretical chapters informed the experimental chapters that led to the successful completion of the Feasibility Trial with IC patients (**FIGURE 17**). The literature review provided a theoretical rationale for the potential use and benefits of BFR-RE in IC patients which contributed to the collaboration with Consultant Vascular Surgeon Mr Shah Nawaz which was essential for NHS ethical approval and recruitment of patients. Additionally, the literature review highlighted key considerations into BFR-RE protocol designs which informed the decisions of protocols and procedures described in the General Methods Chapter and used in the Experimental Chapters.


Literature Review
Physiological mechanisms contributing to the functional decline in IC patients and the acute and chronic responses to BFR-RE.
General Methods
Protocols and procedures to be employed
Experimental Chapter 1
Acute perceptual, affective and physiological responses to low-load resistance exercise with BFR in comparison to low load and moderate load resistance exercise in young and older adults.
Experimental Chapter 2
Test-retest reliability of physical function test battery in patients with IC.
Experimental Chapter 3
Load-load resistance exercise with BFR in Patients with IC: Feasibility trial

The aim of the first experimental chapter was to scope and explore the acute perceptual, affective, and physiological responses to BFR-RE to pilot the BFR-RE protocol in our research laboratory. This Experimental Chapter was critical in the BFR-RE protocol design for patients with IC which led to the alteration of exercise volume to reduce the pain response to BFR-RE when prescribed to IC patients. The aim of the second Experimental Chapter was to examine the reliability of assessments used in this thesis. The assessments were chosen to assess haemodynamic change (ABPI), walk performance (6MWT), lower limb strength (MVT) and lower limb muscle size (VL-MT). The findings enabled the calculation of the smallest worthwhile change which was critical for the interpretation of the effects of BFR-RE in the feasibility study which was not powered to test significant differences. The findings of the first and second Experimental Chapter contributed to the BFR-RE protocol design which was found to be tolerable for the patient and the evaluation of the efficacy of BFR-RE which was found BFR-RE to be potential beneficial to IC patients.

7.5 Limitations

The individual limitations of each Experimental Chapter have been set out in the corresponding chapters. However, there are some overarching limitations to the thesis.

The research does not include a walk exercise group which is the gold standard exercise prescription for IC patients. This would enable the investigation of the extent BFR-RE is safe, adhered to, and efficacious in comparison to walking training. The decision not to include a walk exercise group was twofold (1) it is

important to first discover whether BFR provides an additional benefit to low load resistance exercise as a proof of concept prior to comparisons between other modes of exercise. (2) Resources available to the project meant the Feasibility Trial (Chapter Six) was limited to the inclusion of two exercise groups (BFR-RE and matched resistance exercise without BFR).

The research programme was heavily impacted by the COVID-19 pandemic which affected University procedures and clinical services, placing significant time constraints on the Feasibility trial (Chapter Six). To manage this challenge the exercise programme was reduced from 12 weeks to 8 weeks. As a result, the adaptations that could occur from the exercise programme may be limited with the reduced training exposure. Additionally, due to the time constraints placed on the project, Post Intervention interviews which aimed to explore the acceptability of the exercise programme and identify barriers and facilitators to exercise was not completed, despite ethical approval. Such qualitative analysis would provide a more comprehensive evaluation into the feasibility of a fully-power randomised control trial that could inform the improvement of the research design.

The Experimental Chapters included in the thesis were attempting to scope and explore the feasibility of the proposed methods and interventions, therefore no definitive clinical recommendations can be made, and further work will be needed before the wider use of BFR-RE is recommended.

7.6 Future Directions

The next priority for future research on this topic is the progression to a full-scale definitive trial. Such a trial should engage stakeholders, namely patients and NHS collaborators, from the outset. Meaningful engagement with stakeholders at each stage of the research will maximise the potential of developing the intervention to be more effective for real-world applications (Skivington et al., 2021).

Economic considerations should be a component of any future trial. Early engagement of economic expertise will help identify the scope of cost effectiveness of the intervention (Barnett et al., 2020). To improve the cost effectiveness of the intervention, future studies may wish to consider amending the research design to group BFR-RE sessions from one-to-one sessions. Increasing the supervisor to patient ratio will be more efficient, but also offer social support to the patients which is an important element for intervention design (Gorely et al., 2015).

Future work may wish to incorporate education workshops that aim to promote physical activity. The benefits of exercise are not fully understood in many IC patients (Harwood et al., 2017) and such workshops would benefit patients beyond the exercise programme and may encourage engagement with the intervention.

Future exercise interventions in this area should consider whether they are accessible to those from disadvantaged socioeconomic groups. Socioeconomic inequalities have a significant impact on PAD resulting in higher prevalence and

poorer outcomes (Pande & Creager, 2014). Socioeconomically disadvantaged groups are more likely to experience adverse health outcomes from inactive lifestyles and have low response rates and high attrition in exercise interventions (Craike et al., 2018). This may require active and targeted recruitment, engagement with community stakeholders and organisations and ensuring research personnel are well trained to match the population of interest in order to encourage accessibility and appealability to these groups (Carroll et al., 2011).

Future studies using BFR-RE with patients with IC should examine the potential mechanisms which exercise performance may be improved. Therefore, including a larger set of outcomes which assesses cardio-respiratory physiology (e.g. $\dot{V}O_2$ kinetics), haemodynamics (e.g blood flow and flow mediated dilatation), blood analysis (e.g mitochondrial number and function), muscle architecture (e.g. pennation angle and fascicle length), and muscle function (e.g. rate of force development and rates of fatigue).

7.7 Reflection

The PhD programme has been profoundly valuable and rewarding. I understand the value of the PhD because it is evidence of resilience, commitment, collaboration and effort. Every attribute of my academic ability has developed because of exemplary guidance and supervision I was fortunate to receive. The programme has given me the learned experience of designing, planning and implementing a clinical trial. I have learned how to effectively work with and for organisations, pre-empt challenges and barriers and adapt to challenges when they are unavoidable.

The COVID-19 pandemic presented an unprecedented challenge to people's lives. The dramatic loss of life was frightening, and the social isolation contributed to the decline in many people's mental health. With lockdown prohibiting face to face research indefinitely, the PhD programme had to make several substantial compromises to account for its impact. Despites the compromises, the project was successful in recruiting 30 patients with IC, delivering an exercise programme allowing sufficient data to be collected to address the research objectives and questions. Therefore, despite challenges posed on the PhD programme, the overarching objective of the thesis was addressed, I developed my academic skills, and gained valuable experience to progress me in my academic career.

7.8 Thesis Conclusions

The Experimental Chapters presented in this thesis are a novel contribution to knowledge that aimed to scope and explore the feasibility of BFR-RE in patients with IC. Examination into the acute perceptual, affective and physiological responses to BFR-RE found BFR-RE is more painful than matched exercise performed at low load and moderate load without BFR which is an important consideration for the implementation of BFR-RE. Despite the increase in pain, there was no detrimental impact on affective response, and positive affect, negative affect, fatigue and tranquillity were comparable between the three exercise conditions. Such parameters are important for exercise adherence and participants intentions to engage with exercise. Additionally, the findings highlighted single joint resistance exercise induces significantly higher perceptual

and physiological responses than multi-joint resistance exercise when matched for volume-load (Sets x reps x %1RM). This finding demonstrates the type of resistance exercise should be careful considered in the exercise programme design when managing the expected perceptual and physiological demand that will occur from resistance exercise prescription. Findings in this thesis indicate excellent reliability of a physical function test battery supporting its use to evaluate IC patients. Analysis from the findings enabled the calculation of the smallest worthwhile change which can be used to interpret the effects of an exercise programme. Lastly, the thesis provided valuable evidence on the safety, feasibility and preliminary efficacy of BFR-RE in patients with IC. The findings indicate that the procedures for recruitment, allocation, and outcome measurements are acceptable and feasible and BFR-RE is safe and tolerable. There is also evidence to suggest that BFR-RE has a beneficial effect on walking performance in patients with IC.

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9 Appendices

Appendix 1: Participant Documents and Proformas

Participant Information Sheet

Title: Relative tolerance of lower-body resistance exercise with blood flow restriction in older adults.

Research Lead: Tom Parkington

You are invited to volunteer for this study which aims to assess the tolerability of lower-body resistance exercise with blood flow restriction by comparing the method to the 'traditional' method of resistance exercise. There is huge potential in exercise with blood flow restriction to improve people's physical ability particularly for those who find conventional exercise challenging. Your involvement in this study contributes to the research lead PhD thesis to inform an exercise protocol to improve functional ability in people with peripheral arterial disease, a type of cardiovascular disease.

What is expected of me if I take part?
If you decide to take part in the study you will be asked to visit the laboratory at Sheffield Hallam University 5 times, with each visit separated by at least 3 days.

Visit 1 - Preliminary Testing (2 hours):
There are three parts to this visit.
Part 1 *- Health screen*
You will be asked to undergo a comprehensive health screen which will assess your BMI, waist circumference, blood pressure, blood cholesterol and blood glucose.
Part 2 *- Determining blood flow restriction pressure*
The researcher will determine what restrictive pressure to use by measuring the pressure which fully restricts blood flow in the legs by using ultrasound techniques.
Part 3 *- Determining training intensities*
In order to prescribe relative exercise intensities the researcher will take you through a progressive exercise protocol to estimate your maximum strength.

Visit 2 - Practice Trials (1 hour):
During this visit you will have the opportunity to experience the exercises under the prescribed training loads under all the different conditions (low-load with blood flow restriction, high-load without blood flow restriction and a control condition of low-intensity exercise without blood flow restriction).

Visit 3 to 5 - Exercise Trials (1 hour):
During these visits you will be asked to undertake leg press and leg extension exercise under one of the 3 conditions (low-load with blood flow restriction, high-load without blood flow restriction and a control condition of low-intensity exercise without blood flow restriction).
During the exercise your heart rate will be monitored through a chest belt, blood pressure will be assessed and your ratings of effort, discomfort, mood and soreness will assessed by short questionnaires

What is blood flow restriction exercise?
Blood flow restriction exercise is a method whereby a blood pressure cuff is applied around the upper leg and inflated reducing the amount of blood flow leaving the leg.
Is it safe?
Blood flow restricted exercise is well tolerated and regarded as safe in a healthy and active population. It is advised that people who are more at risk of adverse events during exercise (for example people with cardiovascular disease) only perform exercise with blood flow restriction with a trained practitioner. Participants in this study will always be supervised.
Is it beneficial?
The beneficial effects of exercise with blood flow restriction to improve muscle strength and size in older adults are unprecedented. The key benefit is it can be performed at a low intensity (20% of one repetition maximum) and promote beneficial effects similar to resistance exercise performed at much higher intensities (80% of one repetition maximum). This has proven useful for people who struggle lifting moderate to heavy loads due to joint or muscle weaknesses.
What can I expect?
The feeling of exercise with blood flow restriction is unique. Because the method involves restricting blood leaving the legs, they become swollen or 'pumped'. This may give increased feelings of effort and hotness and early onset of exhaustion. There is a sense of instant relief from those feelings when the cuff is deflated.

How will I benefit from volunteering to participate in this study?
Your involvement in the study will contribute to data that will help practitioners understand the tolerance of different resistance exercise methods which will inform exercise prescription to maximise adherence to exercise programmes.
Participants may also benefit from a comprehensive health screen assessment including, body composition, blood pressure, blood cholesterol and glucose of which you will be able to discuss the results with the researcher.
If participants would like to continue resistance exercise the researcher will discuss and offer sessions that are suitable.

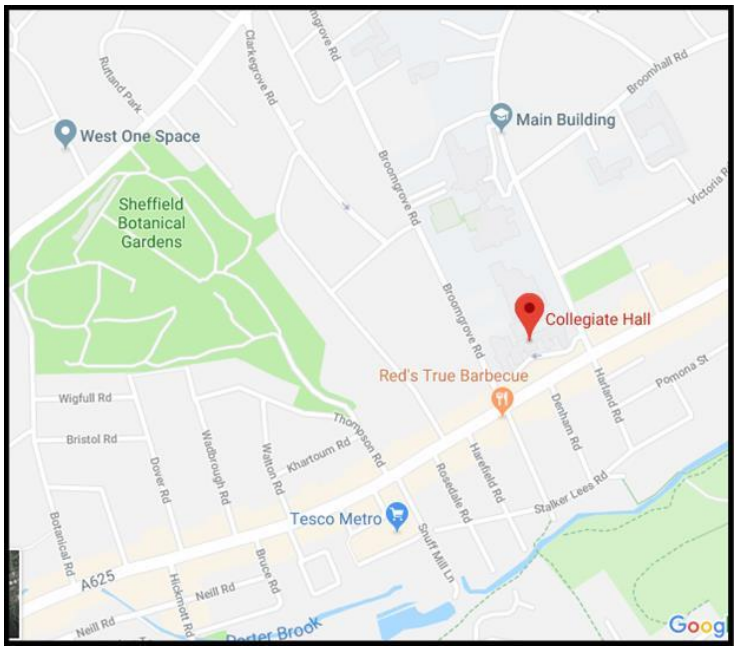
Am I suitable to partake in the study?
If you are a healthy adult ≥ 60 years you are likely to be a suitable volunteer. The researcher will ask some questions and screen to ensure eligibility.
You are not eligible if you meet any of the following criteria.

- A wheelchair user or have a walking aid.
- High blood pressure (>140/90 mmHg). This will be measured by the researcher.
- Taking heart medication.
- Current smoker.
- Diagnosed peripheral arterial disease.
- Diagnosed heart disease.
- Diagnosed lung disease.
- Diagnosed liver disease.
- Knee arthritis.
- Neuromuscular disease.
- Terminal disease.
- Diabetic.
- Had a heart attack or stroke.
- Deep vein thrombosis
- Major surgery in the last 6 months.
- Bone fracture in the lower body in the last 6 months.

Is my data confidential?
Your data collected in this study is anonymous and no one other than the researcher will be able to connect data collected to you.

What if I change my mind during the study?
It is important for you to know that you do not need to take part in this study and that you have the right to withdraw at any time without providing an explanation. You may also withdraw the data collected up to the point of a manuscript being drafted but from this point it will not be possible to do so.

Where is the study taking place?
The study will take place at Sheffield Hallam University, Collegiate Hall, Collegiate Crescent, S10 2BP in a controlled private space.



Thank you for taking the time to read this information sheet and to consider this study.

If you would like further information please contact the principle researcher Tom Parkington via t.parkington@shu.ac.uk or the chief investigator of this research David Broom via d.r.broom@shu.ac.uk or 01142 254369.

Participant Consent Form

Research Title: Tolerability of lower-body resistance exercise with blood flow restriction in older adults

Researcher: Tom Parkington

Please answer the following questions by ticking the response that applies

		YES	NO
1.	I have read the Information Sheet for this study and have had details of the study explained to me.	☐	☐
2.	My questions about the study have been answered to my satisfaction and I understand that I may ask further questions at any point.	☐	☐
3.	I understand that I am free to withdraw from the study within the time limits outlined in the Information Sheet, without giving a reason for my withdrawal or to decline to answer any particular questions in the study without any consequences to my future treatment by the researcher.	☐	☐
4.	I agree to provide information to the researchers under the conditions of confidentiality set out in the Information Sheet.	☐	☐
5.	I wish to participate in the study under the conditions set out in the Information Sheet.	☐	☐
6.	I consent to the information collected for the purposes of this research study, once anonymised (so that I cannot be identified), to be used for any other research purposes.	☐	☐
7.			

Participant's Signature: _____ Date: _____

Participant's Name (Printed): _____

Contact details: _____

_____

Researcher's Name (Printed): _____

Researcher's Signature: _____

Centre of Sport and Exercise Science
Sheffield Hallam University
Collegiate Hall
Collegiate Crescent
Sheffield S10 2BP
Date:

Dear

We hope this letter finds you well. At Sheffield Hallam University and with support from Sheffield Teaching Hospitals we are undertaking an exercise study to determine the effects of an 8-week lower body blood flow restricted resistance exercise programme to improve leg strength and walking ability in people with peripheral arterial disease.

There are many physical benefits to blood flow restricted resistance exercise, like increased strength, muscle size, and improved vascular function. Research is now being done in patients with heart disease and stroke, but this will be the first study to use this exercise method to peripheral arterial disease, hence the reason for contacting you.

Our research team invites you to participate in this study because you have peripheral arterial disease as determined by Mr Shah Nawaz, a Consultant Vascular Surgeon at Sheffield Teaching Hospitals, and our collaborating physician for this project. Please find enclosed a Participant Information Sheet, which describes the study in detail and answers many frequently asked questions. If you would like to talk more about the study or would be interested in participating, please call or email from the details below. The study opened in January 2021 and you can start your involvement from this point. Dates, days and times can be arranged to ensure your involvement is convenient for you.
Please be aware that Public Health England guidance will be followed at each visit to protect both participants and researchers from COVID-19 infection/transmission. Please find enclosed a Covid-19 Information Sheet, which describes the measures in place at Sheffield Hallam University for Covid-19 protection.

It is important to note that there is no pressure to participate in this study. If you do not respond to this letter, then you will not be contacted further.
Yours sincerely,

Tom Parkington
Tel: [redacted]
Email: t.parkington@shu.ac.uk

TITLE OF RESEARCH STUDY:
Effect of low-intensity lower-body resistance exercise with blood flow restriction on functional performance in people with peripheral arterial disease: A feasibility study

You are invited to volunteer for our exercise study. Before you decide whether you would like to take part please take some time to read this document that provides full details of the study, so it is clear what you would be asked to do, and the risks involved. If something is not clear or you have any questions, please contact us to talk it through. Our contact details can be found at the end of this document.

What is the study about?

Peripheral arterial disease is a type of cardiovascular disease where a build-up of fatty deposits in the arteries restricts blood supply to the legs, which can cause pain that can affect walking ability and lead to reduced leg muscle size and strength. Resistance exercise with blood flow restriction is now popular in clinical practice as a method of exercise to increase muscle size and strength. However, this method of exercise has not been used before in people with peripheral arterial disease. Therefore, it is unknown if the method of exercise is feasible or what effect it will have on muscle size or strength in people with peripheral arterial disease. The aim of this study is to determine rates of patient screening, eligibility, recruitment, retention, attendance, and adverse events following a 8-week lower-body blood flow restricted resistance exercise programme. This study will also explore effects and trends of the intervention on functional performance measures; 6-minute walk test, maximal leg strength and short physical performance battery.

Why have you asked me to take part?

We have asked you to take part because you have peripheral arterial disease as determined by Mr Shah Nawaz (Consultant Vascular Surgeon) and are therefore eligible to participate in this study.

What are the criteria to be able to participate in this study?

Men and women who have been diagnosed with peripheral arterial disease who are physically able to perform leg press and leg extension exercise are able to participate in this study. Eligible participants must be able to commit to 2 visits a week for 10 weeks at Sheffield Hallam University Collegiate Hall. People will not be able to participate in the research study if they meet any of the following criteria.

- Under 18 years of age
- Unable to commit to the visiting requirements
- If peoples walking is impaired by a non-peripheral arterial condition (for example cerebral palsy or multiple sclerosis).
- People with severe peripheral arterial disease who experience pain in their legs when resting or have leg ulcers.
- People who have sharp pain in their joints when extending their legs.
- Women who are pregnant.
- People with dementia.
- People who have had a heart attack, stroke, or thrombosis.
- People who have had major surgery in the previous 6 months or have major surgery planned during the study period.

What is exercise with blood flow restriction?

Blood flow restriction is a method where exercise is performed with pressure cuffs applied around the upper part of the thighs. The cuffs are inflated during exercise at a moderate pressure which partial reduces blood supply to the legs but more significantly restricts blood flow leaving the legs. This causes blood to stay within the legs making the muscles work harder than what would be usually expected.

This means exercise can be performed at a low intensity. Research has shown exercising at low intensity with blood flow restriction can increase muscle strength and size similar to exercise that is performed at higher intensities. However, because this method has not been used in people with peripheral arterial disease before the research team does not know if the method will be more difficult or cause more pain, discomfort, and harm than what is normally expected during exercise.

Is it safe? How does resistance exercise with blood flow restriction feel?

There are known risks from exercising with blood flow restriction. Incidence of muscle soreness is 1 in 5 people, feeling faint or dizzy is 1 in 6 people, muscle damage which may need medical care is 1 in 50 people, superficial thrombophlebitis is 1 in 200 people, deep vein thrombosis is 6 in 1000 people and pulmonary embolism is 1 in 1000 people. However, there is no evidence to suggest that undertaking exercise with blood flow restriction is more harmful than conventional resistance exercise.

Research has examined the effects of blood flow restricted resistance exercise in people heart disease and found no change in blood markers for blood clot generation or clot formation nor were there reports of any adverse events.

However, the sensations experienced while performing blood flow restricted resistance exercise is different than conventional resistance exercise. During blood flow restricted resistance exercise the exercisers legs may feel hot and more achy than normal and muscles may feel as if they are swollen and tight. This is due to an increased blood in the muscle. These feelings are relieved immediately when the pressure cuff is deflated.

Why do exercise with blood flow restriction over exercising normally?

blood flow restricted resistance exercise is always performed at a low intensity. This is because the cuff pressure around the legs causes the muscles to work harder than they usually would therefore there is no need for heavier loads, which is better hip and knee joints. Also, there is evidence that suggests blood vessels benefit from blood flow restricted resistance exercise more than conventional resistance exercise, which can have a positive effect on blood pressure.

However, from the research we have already conducted, even though the exercise is performed with less resistance load some people find exercising with blood flow restriction more difficult and discomforting than conventional resistance exercise.

What are the lower-body resistance exercises?

For this study participants would be asked to perform two different types of leg resistance exercises, the leg press (**Fig 2**) and knee extension (**Fig 3**). The leg press is an exercise where the exerciser pushes the resistance load away from themselves using all the muscles in your legs. The knee extension is an exercise where the exerciser uses their thigh muscles to straighten their knee while acting against a resistance weight applied to the lower shin. Both exercises are performed on specific apparatus while seated.

Fig 2: Leg press performed during this study.

Fig 3: Knee extension performed during this study.

What will I be required to do if I volunteer in this study?

You will be asked to visit Sheffield Hallam University's Collegiate Hall 20 times over a 10-week period, which is approximately 2 times a week. This will include two testing sessions (at baseline and post-intervention), a familiarisation session, 16 supervised resistance exercise sessions and a post intervention interview.

If you volunteer to participate in this study, you will be screened through your medical notes by Dr Shah Nawaz, to ensure you are able to participate in the study without any predisposed risk. Following this you will be randomly allocated into one of two exercise groups.

Group 1: This group will perform blood flow restricted resistance exercise during supervised sessions.

Group 2: This group will perform lower-body resistance exercise without restriction during supervised sessions.

You will not know your group allocation until consenting to participate in the study and will not have influence in the choice of group you are in nor will your group change during the study period.

The order of visits are as follows.

- Visit 1 (week 1): Baseline testing
- Visit 2 (week 1): Familiarisation session
- Visit 3 – 18 (weeks 2 – 9): Supervised resistance exercise sessions (16 sessions in total)
- Visit 19 (week 10): Post intervention testing
- Visit 20 (week 10): Post intervention interview

What can I expect in the testing sessions?

You will complete testing sessions at baseline (week 1) and post intervention (week 10). These testing sessions are important in the study as they allow us to measure the effect of the exercise on your strength. The test sessions will include assessments of ankle-brachial pressure index, muscle size via ultrasound techniques, maximal isometric knee extensor strength, six-minute walk test and timed up-and-go test. The testing session can occur at any time of day, but it is asked the times are consistent for all testing sessions. These sessions will take approximately 2 hours to complete. If unusual findings from the assessments are identified, you will be immediately informed, and it may be advised that you see your GP. In this instance, your participation in the study may be ended for your safety.

Ankle-brachial pressure index
This is an assessment of blood pressure measured at the ankle and arm. It is an assessment used to determine the severity of your peripheral arterial disease. This test will allow us to assess how blood pressure is affected by the exercise intervention.
What are the risks of this test?

- There is a likely risk of discomfort caused by high cuff pressures around your arms and ankles.
- There is an unlikely risk of abrasion and bruising to the skin caused by applying the cuffs around the legs and inflating to high pressures.
- There is an unlikely risk of allergic reaction and anaphylaxis caused by application of ultrasound gel.

Muscle thickness via ultrasound techniques
Muscle thickness of the thigh and calf muscle will be measured via ultrasound techniques. This assessment will allow us to see if there is a change in muscle size caused by the exercise intervention. For this assessment you will be asked to wear shorts.
What are the risks of this test?

- There is an unlikely risk of allergic reaction and anaphylaxis caused by application of ultrasound gel.

Maximal isometric knee extensor strength
The aim of this test is to assess your maximal strength in your legs. You will be seated on specific apparatus. Your leg will be strapped to a strain gauge that does not move. Under instruction of the researcher you will extend your leg to force against the strain gauge at maximal effort for 5 seconds. The apparatus will measure the force your leg can produce. You will be asked to do this for both legs.
What are the risks of this test?
There are several risks caused by exercising to maximum effort detailed below.

- There is a likely risk of muscle soreness following this test.
- There is a possible risk of muscle strain.
- There is an unlikely risk of heart attack and stroke.

Six-minute walk test
During this test you will be asked to walk up and down a marked corridor for 6 minutes with the aim to cover as much distance as you feel comfortable. The researcher will record the distanced you covered and also monitor any pain you may experience.
What are the risks of this test?

- If you have peripheral arterial disease symptoms, there is a very likely risk of discomfort caused by the onset of walking.
- There is an unlike risk of falling caused by loss of balance during walking.
- There is an unlikely risk of muscle strain caused by walking.
- There is an unlikely risk of heart attack, stroke or thrombosis caused by walking.

Timed up-and-go test
This test times how quickly you can rise from a chair walk three metres, return to the chair and sit. This is a clinical assessment of lower body functioning.
What are the risks of this test?

- There is an unlikely risk of falling caused by of loss of balance.

What can I expect in the familiarisation session visit?

Participants in blood flow restricted resistance exercise group will complete a test determine blood flow restriction cuff pressure, test to determine exercise intensity and

then a familiarisation trial to become practiced with the procedures and processes of the study.
Participants in the normal resistance exercise group will complete test to determine exercise intensity and then a familiarisation trial to become practiced with the procedures and processes of the study.

What can I expect in the supervised resistance exercise sessions?

You will undergo supervised exercise sessions with a qualified exercise practitioner. In total, there are 16 exercise sessions over a 8-week period. Your attendance to these sessions is monitored. You will not be asked to complete any unattended exercise sessions past the 8-week period. Each exercise session will last approximately 45 minutes.
In the supervised exercise sessions, you will be first asked to warm up on a static bike for 5 minutes at a light to moderate effort. The exercise sessions consist of leg press and knee extension resistance exercise. Starting with the leg press, you will be asked to perform 1 set of 30 repetitions and 3 sets of 15 repetitions with 30 seconds rest between each set. For knee extension, you will be asked to perform 3 sets of 15 repetitions with 30 seconds rest between each set. Each exercise is performed at 20% of predicted 1 repetition max. Participants will be asked to perform the up and down movements of the exercises in 3 seconds (1.5 seconds up, 1.5 seconds down) with support of a metronome. There will be a five-minute rest period between doing the leg press and knee extension exercise. Heart rate will be monitored and recorded throughout the session using a chest strap. Blood pressure will be measured at rest in the dominant arm and immediately after both exercises for each session via an automated blood pressure monitor.
Throughout the exercise you will be asked of your perception of exertion and perception of discomfort using a scale ranging 1 - 10 before exercise and after every set. 10 minutes after exercising you will be asked of the overall difficulty using a scale.

What are the risks of the supervised exercise sessions?

There are several risks associated with low-intensity lower-body resistance exercise detailed below.

- There is a possible risk of discomfort caused by claudication symptoms from the onset of exercise.
- There is a possible risk of delayed muscle soreness or muscle strain.
- There is an unlikely risk of heart attack, stroke, or thrombosis.
- There is an unlikely risk of rhabdomyolysis (severe muscle damage that can lead to hospitalisation) caused by resistance exercise.

What are the additional risks of the supervised exercise sessions with blood flow restriction?

- There is a likely risk of discomfort that is greater than normal exercise caused by blood flow restriction.
- A possible increase in heart rate and blood pressure greater than normal exercise caused by exercising with blood flow restriction.
- A possible risk of feeling faint or dizzy caused by blood flow restriction cuffs.
- A possible risk of numbness in the legs caused by blood flow restriction cuffs.
- There is an unlikely risk of reperfusion injury (tissue damage caused when blood supply returns to tissue) caused by restricting blood flow.
- There is an unlikely risk of abrasion and bruising to the skin caused by applying the cuffs around the legs and inflating to moderate pressures.

What can I expect in the post intervention interview?
You will be asked to attend a one-to-one interview with the researcher to discuss your experience participating in the research study to inform us of the quality of the intervention. The interview will be recorded using a Dictaphone and will be transcribed. Transcription of the interviews will occur shortly after the interview, and the recordings will be destroyed following transcription. The interview will be a maximum of 1 hour.

What are the benefits of taking part in this study?
You will benefit from 24 supervised exercise sessions that will likely improve your leg muscle strength and size. Your involvement in this study will contribute to data which will inform physicians and exercise practitioners of the possible benefits of resistance exercise with blood flow restriction to improve physical attributes that support daily activities that could lead to improved quality of life in people with peripheral arterial disease.

Do I have to take part?
The decision to take part in this study is solely your choice. If you do decide to take part, it is your right to withdraw from the study at any time without giving a reason. If you would like to participate in the study, please contact a member of the research team from the details at the end of this document or in the invitation letter. If you do not wish to participate or if you do not respond to the invitation letter and you will not be contacted further.

If I decide to participate, will my GP be notified?
With your consent, we will write to inform your GP about your decision to take part.

What if I change my mind and want to withdraw during the study?
You have the right to withdraw from the study at any point. If you do withdraw from the study any data collected from you will be retained and may be used for publications. Though, you may also withdraw the data collected from you up to the point of a manuscript being drafted but from this point it will not be possible to do so.

How will you use the data you will collect from me?
When the study is completed, we will publish the results in a scientific journal and present the findings at conferences. You will receive a summary of our findings.

Is my data confidential?
The data collected in this study is anonymous and no one other than the research team will be able to connect data collected from you to you.

Is my data safe?
The University undertakes research as part of its function for the community under its legal status. Data protection allows us to use personal data for research with appropriate safeguards in place under the legal basis of public tasks that are in the public interest. A full statement of your rights can be found at https://www.shu.ac.uk/about-this-website/privacy-policy/privacy-notices/privacy-notice-for-research. However, all University research is reviewed to ensure that participants are treated appropriately, and their rights respected. This study was approved by University Research Ethics Committee with Converis number ER15905458. Further information can be found at https://www.shu.ac.uk/research/ethics-integrity-and-practice.
You should contact the Data Protection Officer via DPO@shu.ac.uk if:

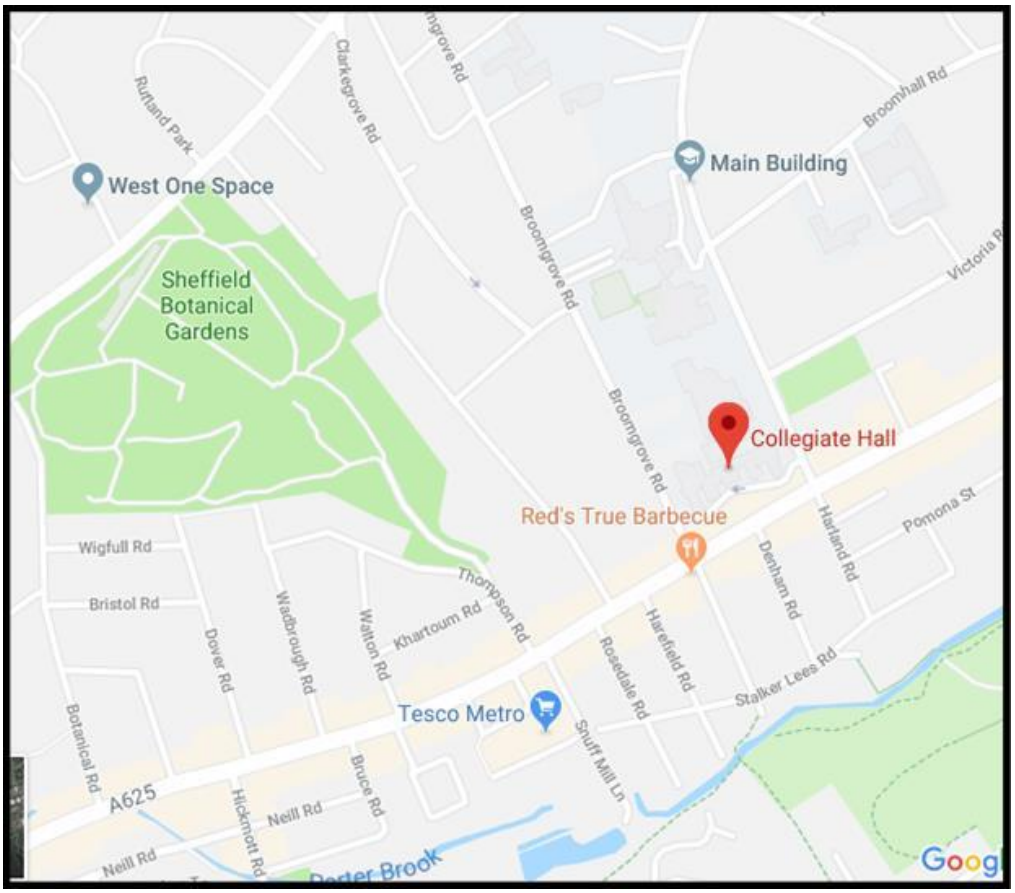
- You have a query about how your data is used by the University

- You would like to report a data security breach (for example, if you think your personal data has been lost or disclosed inappropriately)
- You would like to complain about how the University has used your personal data

What should I do if I have a complaint?
If at any time you feel concerned or have a complaint about how the research is conducted or how you have been treated you can contact the Head of Research Ethics, Professor Ann Macaskill via a.macaskill@shu.ac.uk.

Where is the study taking place?

The study will take place at Sheffield Hallam University, Collegiate Hall, Collegiate Crescent, S10 2BP. All sessions are held in a private and controlled space. Unfortunately travel expenses will not be provided, however free parking is available at the facility. This will have to be arranged in advanced with the researcher following details provided of your car registration number.



How do I volunteer to participate?
If you would like to participate in the study, please contact the research lead Tom Parkington via the details below. If you do not contact Tom, it is assumed you do not wish to participate.

When does the study start?
The study will open in January 2021 and you can start your involvement from this point and dates, days and times can be arranged with Tom to ensure your visits are convenient for you.

This study has received ethical approval from the National Health Service's Health Research Authority and Sheffield Hallam University Research Ethics Committee.

Thank you for taking the time to read this information sheet and to consider taking part in this study.
If you would like further information please contact the research lead Tom Parkington via [redacted] or t.parkington@shu.ac.uk

PARTICIPANT INFORMED CONSENT FORM

TITLE OF RESEARCH STUDY: Effect of low-intensity lower-body resistance exercise with blood flow restriction on functional performance in people with peripheral arterial disease: feasibility study

Please answer the following questions by ticking the response that applies

	YES	NO
8. I have read the Information Sheet for this study and have had details of the study explained to me.	☐	☐
9. My questions about the study have been answered to my satisfaction and I understand that I may ask further questions at any point.	☐	☐
10. I understand that I am free to withdraw from the study within the time limits outlined in the Information Sheet, without giving a reason for my withdrawal or to decline to answer any questions in the study without any consequences to my future treatment by the researcher.	☐	☐
11. I agree to provide information to the researchers under the conditions of confidentiality set out in the Information Sheet.	☐	☐
12. I wish to participate in the study under the conditions set out in the Information Sheet.	☐	☐
13. I consent to the information collected for the purposes of this research study, once anonymised (so that I cannot be identified), to be used for any other research purposes.	☐	☐

Participant's Signature: _____ Date: _____

Participant's Name (Printed): _____

Contact details:

_____

_____

_____

Researcher's Name (Printed): _____

Researcher's Signature: __________

Appendix 2: Ethical Approval

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Shah Nawaz
Consultant Vascular Surgeon
Sheffield Teaching Hospitals
Sheffield Vascular Institute, Old Nurses Home
Northern General Hospital, Herries Road
Sheffield
S5 7AT

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

18 March 2020

Dear Dr Nawaz

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Effect of low-intensity lower-body resistance exercise with blood flow restriction on functional performance in people with peripheral arterial disease: A feasibility study**
IRAS project ID:	**260419**
Protocol number:	**N/A**
REC reference:	**20/YH/0039**
Sponsor	**Sheffield Hallam University**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report

(including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **260419**. Please quote this on all correspondence.

Yours sincerely,
Alex Thorpe

Approvals Manager

Email: approvals@hra.nhs.uk

Copy to: *Dr Keith Fildes, Sheffield Hallam University, Sponsor's Representative*