EXERCISE INTERVENTIONS FOR PATIENTS WITH PERIPHERAL ARTERIAL DISEASE

by

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DISSERTATION ABSTRACT

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Title: Exercise Interventions for Patients with Peripheral Arterial Disease

Peripheral arterial disease (PAD) is atherosclerosis of the arteries outside of the heart and brain, particularly the lower extremities, and represents an advanced burden of cardiovascular disease. Patients with PAD have a high risk of morbidity and mortality. In addition, PAD leads to an accelerated decline in physical function and increased disability in both symptomatic and asymptomatic patients. Evidenced-based guidelines recommend walking in a supervised setting as the primary mode of exercise for patients with PAD. However, many patients are either unwilling or unable to tolerate the exercise due to the symptoms of claudication pain. The primary purpose of this dissertation was to expand on the standard practice and explore novel exercise and other training techniques that could improve the outcomes of patients with PAD.

The study in chapter IV compared a novel combination treadmill and ambulation training protocol (COMBO) with a commonly used standard treadmill only training protocol (STAND) on patients with PAD. This was the first study to compare the difference between two training protocols on six-minute walk test (6MWT) performance in patients with PAD. The improvement in 6MWT total distance did not differ between the COMBO and STAND training protocols. However, both the 6MWT claudication onset distance and claudication onset time were greater in the COMBO group versus the

STAND group. The results of this study suggest that ambulation training may improve 6MWT performance compared treadmill only training in patients with PAD.

The study in chapter V investigated the effect of an active walking warm-up on the results of the 6MWT distance in patients with PAD. The study was the first to assess the effect of an active warm-up on the 6MWT in patients with PAD. The 6MWT total distance did not differ between the WARM-UP and NO WARM-UP conditions. Additionally, neither the 6MWT claudication onset distance nor claudication onset time differed between the WARM-UP and NO WARM-UP conditions. The results of this study suggest that an active warm-up of 10-12 minutes of walking on a treadmill at a workload between 1.4-2.1 METs may not be enough of a stimulus to increase 6MWT distance in patients with PAD.

Chapter VI was a review article intended to explore novel exercise and other interventions that could challenge the current paradigm of exercise training for patients with PAD. This was accomplished by reviewing the literature showing improved outcomes, particularly 6MWT distance, with exercise in patients with PAD, discussing the current state of practice of PAD rehabilitation (SET for PAD), introducing overground ambulation in the supervised clinical setting, reviewing the literature on the effect of acute and chronic passive heating in patients with PAD, and discussing directions for future research with ambulation training and passive heating, two interventions that have shown improvement in 6MWT performance in patients with PAD.

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Harding AW (2023). Special Considerations for Cardiovascular Disease: Valvular Heart Disease and Peripheral Arterial Disease. In *ACSM's Exercise Testing and Prescription: A Companion Textbook for Apparently Healthy and Special Populations*, *Second Edition* (pp. 237-252). Philadelphia, PA: Wolters Kluwer. ISBN-13: 978-1-9751-9707-0.

Harding AW (2021), chapter reviewer. Exercise Prescription of Patients with Various Cardiovascular and Pulmonary Diseases. In *ACSM's Guidelines for Exercise Testing and Prescription*, *Eleventh Edition.* (pp. 226-266). Philadelphia, PA: Wolters Kluwer. ISBN-13: 978-1-975-150-18-1.

Harding AW and Patterson MA (2018). Special Considerations for Cardiovascular Disease: Valvular Heart Disease and Peripheral Arterial Disease. In *ACSM's Exercise Testing and Prescription: A Companion Textbook for Apparently Healthy and Special Populations* (pp. 215-230). Philadelphia, PA: Wolters Kluwer. ISBN-13: 978-1-4963-3879-2.

Kerrigan DJ, Verrill DE, **Harding AW**, Drew K. CEPA 2015 clinical exercise physiology practice survey. *Journal of Clinical Exercise Physiology*. 2017; 6(1):9-16.

Brawner CA, **Harding AW**, Headley SAE, Verrill DE. 2010 Clinical Exercise Physiology Practice Survey, *www.acsm-cepa.org*, 2011.

Holowatz, LA, BL Houghton, BJ Wong, BW Wilkins, **AW Harding**, WL Kenney and CT Minson. Nitric oxide and attenuated reflex cutaneous vasodilation in aged skin. *Am J Physiol Heart Circ Physiol*. 2003; 284:1662-1667.

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To my children Alex and Amy, you are in control of your future. Go get it.

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CHAPTER I

INTRODUCTION

BACKGROUND

Peripheral arterial disease (PAD) is atherosclerosis of the arteries outside of the heart and brain, particularly the lower extremities. Approximately 8.5 million Americans have PAD, including more than 14% of people over 70 years old (Selvin and Erlinger, 2004) and 22% of people over 80 years old (Benjamin *et al*, 2017). This number will continue to grow and become a greater public health burden as the population ages. The major risk factors for PAD are the same as for other cardiovascular diseases with smoking and diabetes by far the most potent risk factors (Murabito *et al*, 1997; Benjamin *et al*, 2017).

Since PAD represents an advanced burden of cardiovascular disease, patients with PAD have a high risk of morbidity and mortality. The risk of stroke, myocardial infarction (Agnelli *et al*, 2020) and mortality (Hirsch *et al*, 2008) is equivalent to or greater than the risk in patients with coronary artery disease. The 10-year mortality risk for patients with PAD ranges from 22-70% depending on age and severity of risk factors (Criqui *et al*, 1992; Feringa *et al*, 2007).

In addition to a high risk of cardiovascular events, PAD leads to an accelerated decline in physical function and increased disability in both symptomatic and asymptomatic patients (McDermott *et al*, 2002; Gardner *et al*, 2007; McDermott *et al*, 2008a). For symptomatic patients, the greatest limitation to activity is ischemic pain in the legs known as intermittent claudication. Claudication originating from PAD typically presents as a cramping or tightness sensation in the lower extremities caused by reduced arterial blood flow that predictably waxes and wanes with exercise and rest. Claudication most often presents itself in one or both calves but can also occur in buttocks and thighs. This discomfort can also present itself in various other forms such as aching, muscular fatigue, weakness, burning, and numbness (AACVPR/VDF, 2010).

It is estimated that only 10-15% of patients with PAD experience classical claudication symptoms (Hirsch *et al*, 2001; McDermott *et al*, 2001), yet asymptomatic patients show the same decline in functional status and have the same risk of morbidity and mortality as symptomatic patients. There could be something in the disease process itself that contributes to this decline or possibly the individual avoids activity that produces pain and only appears to be asymptomatic. Regardless, PAD contributes to functional decline and increased risk of adverse events in both symptomatic and asymptomatic patients (Gardner *et al*, 2008).

The first line of treatment for patients with PAD, and without critical limb ischemia, is exercise and risk factor modification. Evidenced-based exercise guidelines for patients with PAD recommend weight-bearing exercise, specifically walking in a supervised setting (Parmenter *et al*, 2011). However, until recently, the opportunities for patients with PAD to participate in structured exercise programs were limited to patients who could self-pay or who participated in a research study. In 2017, the Center for Medicare and Medicaid Services announced a national coverage determination for Supervised Exercise Therapy (SET) for patients with symptomatic PAD (CMS Decision Memo, 2017). Most SET for PAD services are being provided within cardiac rehabilitation programs due to current infrastructure and staff skill set. To guide the clinician in treating patients with PAD, the American Association of Cardiovascular and

Pulmonary Rehabilitation and Vascular Disease Foundation developed a PAD Exercise Training Toolkit. The toolkit outlines and suggests using a standard training protocol of supervised treadmill walking (AACVPR/VDF, 2010).

STATEMENT OF THE PROBLEM

Multiple review articles and position statements support walking as beneficial and as the primary mode of exercise for patients with PAD (Gerhard-Herman *et al*, 2017; Hamburg and Balady, 2011; Askew *et al*, 2014). In a 1995 meta-analysis looking at exercise in patients with PAD, Gardner and Poehlman (1995) concluded that the optimal exercise program included intermittent walking at near maximal claudication pain. However, compliance is low and dropout rates are high with these types of exercise programs for patients with PAD (Bendermacher *et al*, 2007). Fortunately, a review by Fakhry *et al* (2012) has shown that similar benefits are achieved using low intensity treadmill walking programs for this population.

The American College of Sports Medicine has published guidelines for prescribing exercise to patients with PAD (ACSM, 2022). In addition, the American Association of Cardiovascular and Pulmonary Rehabilitation and Vascular Disease Foundation developed a PAD Exercise Training Toolkit. The toolkit outlines and suggests using a standard treadmill training protocol (AACVPR/VDF, 2010). Both guidelines suggest the treadmill as the preferred mode of exercise for patients with PAD.

Patients with PAD who participate in supervised treadmill exercise programs show greater increases in maximal treadmill walking distance versus patients who participate in unsupervised home-based walking programs or who receive walking advice (Hageman *et al*, 2018). McDermott *et al* (2009) have demonstrated that patients with

PAD show large improvements in maximal treadmill walking time (51%) when participating in supervised treadmill exercise interventions, yet only show minimal improvement (6.4%) in 6MWT distances. Conversely, patients with PAD who completed a home-based over ground walking program have shown an improvement (12%) in six-minute walk test distances nearly double that shown in the treadmill training program (McDermott *et al*, 2013). This suggests there may be a specificity of the training mode such that patients who train on a treadmill show greater increases in treadmill performance measures and patients who train overground show greater improvement in the 6MWT distance.

Treadmill only training protocols are beneficial but may not be the optimal training protocol for patients with PAD and intermittent claudication. The treadmill protocol in the PAD Exercise Training Toolkit (AACVPR/VDF, 2010) includes a short warm-up period of 4-5 minutes and then introduces a training workload that is at or near the ischemic (claudication) threshold. The limited warm-up period and sudden intensity in workload has the potential to compromise performance, increase symptoms, and decrease both compliance to and enjoyment of the exercise. In addition, this protocol focuses on increasing treadmill incline (up to 10% or more) over increasing walking speed. The rationale is that patients with PAD generally walk at slow speeds due to their claudication symptoms and would tolerate a change in incline over a change in speed. In over 20 years of working with this patient population in cardiac rehabilitation, I have observed that patients adapt just as well with speed changes if the increases in workload are gentle and progressive. Using treadmill only walking and including elevation changes not seen in normal daily life may not translate as well to ground walking or to everyday functional capacity.

An ideal exercise training protocol for a patient with PAD would include supervision, an extended warm-up period, progressive increases in workload and overground walking at speeds that mimic normal walking gait. The few studies that have reported the results of supervised ambulation training in the literature have included other modes of exercise in addition to supervised walking (Fahkry *et al*, 2012). Only one randomized controlled trial has included supervised walking as the exclusive mode of training but did not show any treadmill improvement in walking performance versus a control group (Gelin *et al*, 2001). Including ambulation training in a supervised setting for patients with PAD may have the potential to improve six-minute walk test distance and meaningful clinical outcomes to a greater extent than treadmill training alone.

In addition to including supervised ambulation training, an extended warm-up period has the potential to improve the time and workload achieved by patients with PAD during each exercise session, and ultimately, enhance the improvement over the course of a training program. Specifically, an active walking warm-up may improve the results of the 6MWT distance on patients with PAD. Recent research has shown that acutely heating the lower extremities in patients with PAD significantly increases 6MWT distance (Pellinger *et al*, 2019). However, it is unknown how an active warm-up effects the 6MWT distance with any population.

PURPOSES AND HYPOTHESES

This dissertation was conducted with the following purposes and hypotheses:

1. In chapter IV, the purpose of this study was to compare a novel combination treadmill and ambulation training protocol (COMBO) with a commonly used standard treadmill only training protocol (STAND) on patients with PAD. It was hypothesized that the COMBO protocol would prove to be as good or superior to the STAND protocol when measuring the 6MWT distance outcome.
2. In chapter V, the purpose of this study was to quantify the effect of an active walking warm-up on the results of the 6MWT distance on patients with PAD. It was hypothesized that an active walking warm-up of 10-12 minutes would improve 6MWT distance in patients with PAD.
3. In chapter VI, the purpose of this project was to influence the current paradigm of exercise training for patients with PAD by introducing new techniques that could further improve patient outcomes. This was accomplished by writing a review article on novel training techniques for patients with PAD and including suggested directions for future research.

SIGNIFICANCE

The primary goal of this dissertation is to explore novel exercise and other training techniques that can improve the outcomes of patients with PAD. The 6MWT distance is highly correlated with mortality and cardiovascular events in many patient populations including patients with PAD (McDermott *et al*, 2008b; Olin, 2008; de Liefde *et al*, 2009; de Liefde, 2010; Schiano *et al*, 2006). Identifying strategies that can increase the functional capacity of patients with PAD has the potential to significantly decrease mortality and reoccurring cardiovascular events such as myocardial infarction and stroke. The results from the studies and the review article in this dissertation may help influence clinical practice by developing and promoting new training techniques for vascular rehabilitation programs and improving the lives of patients living with PAD.

CHAPTER II

REVIEW OF THE LITERATURE

INTRODUCTION

Peripheral arterial disease represents an advanced burden of cardiovascular disease and contributes to an accelerated decline in functional capacity, and an increase in disability, cardiovascular events, and mortality (Agnelli *et al*, 2020; Hirsch *et al*, 2008) in both symptomatic and asymptomatic patients (McDermott *et al*, 2002; Gardner *et al*, 2007; McDermott *et al*, 2008a). Improving exercise performance in patients with PAD is important to offset the decreased physical activity seen in this population. This chapter will review the literature on walking and non-walking modes of exercise on functional capacity in patients with PAD, the use of the six-minute walk test as a measure of functional capacity and prognosis in patients with PAD, the effect of both an active and a passive warm-up on exercise performance, the use of passive heat on cardiovascular health and function, and the use of passive heat in patients with PAD.

WALKING EXERCISE AND PERIPHERAL ARTERIAL DISEASE

The first line of treatment for patients with PAD, and without critical limb ischemia, is exercise and risk factor modification. Multiple review articles and position statements support walking as beneficial and as the primary mode of exercise for patients with PAD (Gerhard-Herman *et al*, 2017; Hamburg and Balady, 2011; Askew *et al*, 2014). In a 1995 meta-analysis looking at exercise in patients with PAD, Gardner and Poehlman (1995) concluded that the optimal exercise program included intermittent walking at near maximal claudication pain. The literature on exercise walking programs for patients with PAD shows that supervised treadmill exercise programs significantly increase treadmill walking distance and time, and that home-based walking exercise programs improve overground walking, specifically the 6MWT distance, to a greater extent than treadmill walking programs (McDermott, 2017).

Supervised Treadmill Walking

Most studies looking at walking exercise programs for patients with PAD use supervised treadmill walking. Evidence-based exercise guidelines for patients with PAD recommend weight-bearing exercise, specifically walking in a supervised setting using a treadmill (Stewart *et al*, 2002; Parmenter *et al*, 2011), including patients without claudication symptoms (McDermott *et al*, 2009). Multiple societies have published guidelines for exercise training patients with PAD including the American College of Cardiology/American Heart Association (Hirsch *et al*, 2006; Gerhard-Herman *et al*, 2017), the American Association of Cardiovascular and Pulmonary Rehabilitation/Vascular Disease Foundation (AACVPR/VDF, 2010), and the American College of Sports Medicine (ACSM, 2022). Each of these guidelines recommend using supervised treadmill walking to increase functional capacity and to decrease claudication symptoms in patients with PAD.

Multiple review articles have demonstrated that supervised treadmill walking programs significantly increase treadmill walking distance and pain-free walking distance in patients with PAD. A meta-analysis of 21 exercise rehabilitation programs for the treatment of claudication showed that the greatest improvement in pain-free walking distance was achieved in exercise programs using supervised treadmill walking (Gardner and Poehlman, 1995). In these studies, the distance to claudication onset (mean ± SD) increased 179% from 125.9 ± 57.3 meters to 351.2 ± 188.7 meters, and the distance to maximal claudication increased 122% from 325.8 ± 148.1 meters to 723.3 ± 591.5 meters (Gardner and Poehlman, 1995). A review of 22 studies and over 1000 subjects compared supervised treadmill walking programs to usual care or placebo. The supervised treadmill training increased maximal treadmill walking time by over 5 minutes, the pain-free treadmill walking distance by over 82 meters and the maximal treadmill walking distance by over 113 meters (Watson *et al*, 2008).

The aim of another review article was to evaluate the effectiveness of supervised walking therapy for patients with PAD by reviewing only randomized controlled trials (RCTs). This review, which included 25 RCTs and 1054 total patients, compared supervised walking therapy versus noninterventional controls (Fakhry *et al*, 2012). The supervised walking therapy showed an increase in maximal walking distance of 180 meters and an increase in pain-free walking distance of 128 meters compared to controls (Fakhry *et al*, 2012). This review also suggested that protocols emphasizing lower intensity and shorter duration walking may be as beneficial as protocols that emphasize higher intensity and long duration walking. Additionally, similar improvements in total walking distance and in cardiovascular outcomes have been shown in both asymptomatic patients and in patients with atypical leg symptoms other than intermittent claudication (McDermott *et al*, 2009).

Supervised Treadmill Walking Compared to Medical Treatments

Supervised treadmill walking improves treadmill walking performance more than any other outcome (McDermott *et al*, 2014) and has also been shown to confer equal or greater improvements in treadmill walking distance compared to both pharmacological treatment and endovascular revascularization. Cilostazol, the only FDA approved medication for the treatment of PAD, appears to improve treadmill walking distance by 25-40% (Gerhard-Herman *et al*, 2017). Comparatively, supervised walking therapy improves treadmill walking distance by 50-100% (Fakhry *et al*, 2012).

The CLEVER (Claudication: Exercise Versus Endoluminal Revascularization) trial has shown that a program of supervised treadmill exercise improves maximal treadmill walking time at 6-month follow-up in patients with PAD to a greater extent than endoluminal revascularization and both groups improved over controls (Murphy *et al*, 2012). However, at 18-month follow-up supervised exercise walking was not significantly different than endoluminal revascularization, and both groups were still better than controls (Murphy *et al*, 2015).

Supervised Versus Unsupervised Walking Therapy

The efficacy of supervised exercise therapy has also been compared to unsupervised exercise therapy for patients with PAD. A 2013 Cochrane Database review, which included 14 studies and 1002 total patients, compared the outcomes of supervised versus unsupervised exercise therapy (Fokkenrood *et al*, 2013). All studies in the review used a treadmill walking test for the primary outcome measures. Patients in the supervised exercise programs showed a greater improvement in both pain-free walking distance and maximal walking distance at three and six months when compared to patients in an unsupervised exercise program. The difference in maximal walking distance between the two groups was approximately 180 meters (Fokkenrood *et al*, 2013).

There is also evidence that providing supervised exercise therapy in a community-based setting is just as effective as supervised exercise therapy in a clinic-based setting.

The results of a cohort study of 56 patients with PAD participating in a community-based supervised exercise therapy program (Bendermacher *et al*, 2007) was compared to a Cochrane Database review of patients participating in supervised exercise programs in a clinic setting (Bendermacher *et al*, 2006). The exercise program consisted primarily of treadmill walking to maximal claudication pain (Bendermacher *et al*, 2007). Patients in the study increased their claudication onset distance by 187% at 3 months and 240% at 6 months and increased their maximal walking distance by 142% at 3 months and 191% at 6 months (Bendermacher *et al*, 2007). The study continued for 12 months but used 6-month data because most of the studies in the review were limited to 6-month follow-up (Bendermacher *et al*, 2007). The improved treadmill walking outcomes in the community-based supervised exercise therapy program were at least as effective as the improvements shown in previous supervised exercise programs in a clinical setting (Regenteiner *et al*, 1997; Savage *et al*, 2001; Degischer *et al*, 2002; Cheetham *et al*, 2004).

Home-Based Walking

Since 2017, patients with PAD have had the opportunity to participate in medically supervised exercise programs, called Supervised Exercise Therapy (SET) for patients with symptomatic PAD, and have Medicare or commercial insurance cover the cost of the program (CMS Decision Memo, 2017). However, until referrals to SET for PAD becomes standard practice, home-based exercise programs have the potential to be become adjunctive treatment or the only treatment for patients who may otherwise not participate in SET for PAD.

Many earlier studies showing supervised exercise therapy is superior to home-based walking programs were small studies (Regenteiner *et al*, 1997; Savage *et al*, 2001; Degischer *et al*, 2002; Cheetham *et al*, 2004). Since 2011, three larger randomized trials have shown that home-based walking programs can improve walking outcomes in patients with PAD (McDermott *et al*, 2017). Gardner *et al* (2011) randomized 119 patients with PAD into three groups: supervised treadmill walking, home-based walking or a control group. The exercise groups walked three times per week for up to 40-45 minutes. At the 12-week follow-up, both exercise groups significantly improved pain-free and their maximal treadmill walking times but did not differ from each other. The control group did not improve and showed a trend toward decreasing both pain-free and maximal treadmill walking time (Gardner *et al*, 2011).

In another trial by Gardner *et al* (2014), 180 patients with PAD were also randomized into three groups: supervised treadmill walking, home-based walking or an attention control group that performed light resistance exercise primarily of the upper extremity. The walking groups walked three times per week for up to 40-45 minutes. At the 12-week follow-up, both walking groups significantly improved peak treadmill walking time and six-minute walk test (6MWT) performance over the control group. The supervised treadmill walking group significantly improved peak treadmill walking time over the home-based walking group, and the home-based walking group significantly improved 6MWT performance over the supervised treadmill walking group (Gardner *et al*, 2014), highlighting the specificity of training.

A third randomized trial of home-based walking included both symptomatic and asymptomatic patients with PAD (McDermott *et al*, 2013). The Group Oriented Arterial

Leg Study (GOALS) randomized 192 patients with PAD to a home-based exercise group with cognitive behavior intervention or to a control group. At six-month follow-up, the control group control had an 11.1-meter decrease in 6MWT distance while the home-based walking with behavior intervention group showed a clinically significant improvement of 42.4 meters. This was a difference of 53.5 meters between the two groups. The home-based exercise with behavior intervention group also showed a significant improvement in pain-free and maximal treadmill walking time compared to the control group (McDermott *et al*, 2013).

However, a fourth randomized trial showed no benefit to a home-based walking program when compared to an attention control group. Collins *et al* (2011) randomized 145 patients with PAD and diabetes to a behavior intervention group or an attention control. The intervention group attended once weekly exercise sessions with an instructor and other participants and instructed to walk at home three times weekly for up to 50 minutes. The intervention group received biweekly calls providing feedback on their walking progress. The control group received biweekly calls discussing blood pressure, blood glucose and cholesterol levels. At six-month follow-up, there was no difference in treadmill walking performance between the intervention and the control groups (Collins *et al*, 2011). Additionally, a more recent randomized trial using a combination of telephone coaching and a wearable activity monitor showed no change in 6MWT distance during a nine-month follow-up (McDermott *et al*, 2018).

Although supervised exercise training has shown greater improvements in walking performance, home-based exercise programs may still provide some benefit to patients with PAD. The results of the three randomized trials that showed benefits of home-based exercise programs have led the American Heart Association/American College of Cardiology practice guidelines to give home-based exercise for patients with PAD a Class IIa, Level of Evidence A recommendation (Gerhard-Herman *et al*, 2017).

Supervised Ambulation Training

The literature on supervised walking therapy for patients with PAD includes almost exclusively treadmill training. Conversely, the research on overground walking training includes almost exclusively unsupervised, home-based training. Six randomized controlled trials have reported the results of overground ambulation training in a supervised setting and all used treadmill testing for the primary walking outcomes (Fakhry *et al*, 2012). Four of these studies used other modes of exercise training in addition to overground walking, including upper and lower body exercises, and including both active and passive leg exercises (Dahllof *et al*, 1974; Tisi *et al*, 1997; Hobbs *et al*, 2006; Hobbs *et al*, 2007). One study used polestriding as the mode of exercise (Langbein *et al*, 2002). Including other modes of exercise or assistive devices with walking (e.g., polestriding) makes it difficult to truly measure the impact of supervised walking therapy. Lastly, only one trial used overground walking exclusively in a supervised setting (Gelin *et al*, 2001). This study compared a surgical intervention to supervised exercise and a control group. Only the surgical intervention group showed improvement in treadmill workload and distance, leg blood flow, and leg blood pressure. The supervised exercise and control groups did not improve in any of the outcome measures. The authors concluded that supervised exercise training offered no benefit compared to controls (Gelin *et al*, 2001). This study appears to highlight the importance of the specificity of training and using the appropriate outcome measure for functional capacity.

ALTERNATE EXERCISE INTERVENTIONS AND PERIPHERAL ARTERIAL DISEASE

The term "supervised exercise therapy" in the literature is generally equated with or assumed to mean walking as the mode of exercise. It has been mentioned that the recommended mode of exercise for patients with PAD should be walking (Gerhard-Herman *et al*, 2017; Hamburg and Balady, 2011; Askew *et al*, 2014). However, other modes of exercise training, including lower and upper limb ergometry and resistance training, have shown to improve patient outcomes (Treat-Jacobson *et al*, 2019). Passive stretching can also increase walking distance in patients with PAD (Hotta *et al*, 2019).

Lower Extremity Ergometry

Three studies have assessed the effect of lower extremity ergometry on walking performance in patients with PAD (Sanderson *et al*, 2006; Walker *et al*, 2000; Zwierska *et al*, 2005). In each study, cycle ergometry was used as the mode of exercise. Sanderson *et al* (2006) randomized 41 patients with PAD into three groups: treadmill walking, leg cycling, or a control group. After six weeks, the treadmill walking group significantly improved treadmill walking performance compared to both the leg cycle group and the controls. Peak walking distance was 215 m, 43 m and 16 m and the claudication onset distance was 174 m, 16 m and 49 m in the treadmill walking group, the leg cycle group, and the controls, respectively (Sanderson *et al*, 2006).

Walker *et al* (2000) and Zwierska *et al* (2005) both used a shuttle walk test to measure walking performance and showed greater increases in peak walking distance (50% and 31%, respectively) and claudication onset distance (93% and 57%, respectively) in the leg cycle groups when compared to controls.

Upper Extremity Ergometry

Walker *et al* (2000) and Zwierska *et al* (2005) also included an upper extremity ergometry group in their leg cycling studies. Additionally, Tew *et al* (2009) compared arm cycling to a control group. In each of these studies, subjects in the arm ergometry group performed 20 minutes of exercise twice weekly for 12 to 24 weeks. Collectively, the arm ergometry groups showed an average increase of 30% in peak treadmill walking distance and 50% in claudication onset distance.

The Exercise Training for Claudication study (Bronas *et al*, 2011; Treat-Jacobson *et al*, 2009) randomized 41 patients with PAD to supervised treadmill walking or arm ergometry alone or in combination versus controls. The treadmill group showed the greatest improvement in peak treadmill walking distance compared to the arm cycle group and the controls (69%, 53% and 12%, respectively). However, the arm cycle group showed the greatest improvement in claudication onset distance compared to the treadmill group and the controls (82%, 54% and 3%, respectively).

Since the lower extremity and upper extremity cycle training were not specific to the task of walking, this would suggest that systemic cardiovascular adaptations play a role in contributing to the improvement in walking performance with these modes of exercise training in patients with PAD (Parmenter *et al*, 2015; Treat-Jacobson *et al*, 2009).

Resistance Training

Three studies have compared the effect of resistance training versus treadmill training on walking performance in patients with PAD. All three studies showed that resistance training improved treadmill walking distance. One study showed that treadmill training was superior to resistance training (Hiatt *et al*, 1994). The two other studies showed no difference in treadmill or 6MWT maximal distance or claudication onset distance between training groups (McDermott *et al*, 2009; Ritti-Dias *et al*, 2010). Another study compared high-intensity resistance training (up to 80% of 1-repetition maximum) to low-intensity resistance training (up to 30% of 1-repetition maximum) and controls. After 26 weeks, only the high-intensity group improved 6MWT maximal distance and claudication onset distance (Parmenter *et al*, 2013). This study also showed that changes in 6MWT claudication onset was significantly and independently related to changes in bilateral calf endurance and changes in 6MWT maximal distance was significantly and independently related to changes in bilateral hip extensor endurance (Parmenter *et al*, 2013).

Passive Stretching

In a recent study, Hotta *et al* (2019) evaluated the effect of passive calf stretching on walking performance and vascular function in patients with PAD. Thirteen patients with symptomatic PAD were randomized to either 4 weeks of passive stretching or 4 weeks of no stretching, followed by cross-over to the other intervention. The passive stretching included ankle dorsiflexion splinting at home for 30 minutes 5 days per week. After 4 weeks of passive calf muscle stretching, flow-mediated dilation (FMD, a frequently used noninvasive assessment of endothelial function that is discussed in more detail below under "Microvascular Function") and 6MWT maximal distance significantly improved compared to the control condition (Hotta *et al*, 2019).

SIX-MINUTE WALK TEST AND PERIPHERAL ARTERIAL DISEASE

Improving exercise performance in patients with PAD is important to offset the decreased physical activity levels seen in this population, which strongly predicts a high all-cause mortality risk (Garg *et al*, 2006; Gardner *et al* 2008). Functional assessment tools, such as the six-minute walk test (6MWT) and treadmill walking time, are associated with risk of cardiovascular events and mortality in patients with PAD (McDermott *et al*, 2008b; Olin, 2008; de Liefde *et al*, 2009; de Liefde, 2010; Schiano *et al*, 2006). The six-minute walk test is more closely associated with daily physical activity levels than the treadmill test (McDermott *et al*, 2008c), and is also more sensitive to changes in functional mobility and decline (McDermott *et al*, 2011). There is very little day-to-day variability or learning effect with repeated 6MWT. Montgomery and Gardner (1998) conducted two 6-minute walk tests on patients with PAD one week apart. The distance covered was similar between tests (350m ± 78m vs. 360m ± 73m). They reported an extremely high reliability coefficient (R = 0.94) and a low coefficient of variability (10.4%). Gardner *et al* (2001) and McDermott *et al* (2008b) have also shown no learning effect with repeated 6MWT in patients with PAD.

Patients with PAD respond well to exercise training with clinically meaningful improvement in 6MWT distance. Gardner and colleagues used two formulas to calculate the smallest threshold of change considered to improve a patient outcome. An increase of 30m in 6MWT distance represents a moderate clinically meaningful improvement (Gardner *et al*, 2018). McDermott *et al* (2009) showed that 24-weeks of supervised treadmill exercise increased 6MWT distance 35.9m (range 15.3m to 56.5m) in patients with PAD compared with matched controls. In a population of patients with PAD, McDermott *et al* (2011) have shown that changes in 6MWT distance correlate with clinically meaningful outcomes such as mobility loss and mortality. Patients with PAD completed a 6MWT at baseline, at 1 year and at 2 years. Patients were categorized into tertiles based on 6MWT distance changes. During follow-up at a median of nearly 4 years, patients with the greatest decrease in 6MWT distance had the highest mobility loss, mortality, and cardiovascular disease.

Collectively, these results demonstrate that interventions that increase functional capacity, specifically 6MWT distance, can decrease mortality and improve health outcomes in patients with PAD.

WARM-UP AND EXERCISE PERFORMANCE

To offset the accelerated decline in physical function and increased disability seen in both symptomatic and asymptomatic patients with PAD (McDermott *et al*, 2002; Gardner *et al*, 2007; McDermott *et al*, 2008a), walking exercise appears to confer the greatest benefit (Gerhard-Herman *et al*, 2017; Hamburg and Balady, 2011; Askew *et al*, 2014). Any opportunity to enhance the increase in functional capacity of patients with PAD could significantly improve the health outcomes in this deconditioned population. One potential strategy to optimize the benefit of walking training could be the inclusion of an effective warm-up. Warm-up prior to exercise can be categorized as either active or passive.

Active Warm-Up

Warm-up is universally practiced and thought to be critical for optimal exercise and athletic performance; however, the literature supporting this view is limited or conflicting (Bishop, 2003a; Bishop, 2003b). Active warm-up includes exercise, such as jogging, cycling or calisthenics, and is the most common form of warm-up.

Short-term exercise performance (<10 seconds), such as jumping, sprinting or tests of isometric strength, has been shown to improve most when warm-up increases muscle temperature, T_m, (Binkhorst *et al*, 1977; Ranatunga *et al*, 1987) but does not deplete high-energy phosphate stores (Hirvonen *et al*, 1987). Saltin *et al* (1968) showed that T_m rapidly increases within 5 minutes of exercise onset, plateaus after 10-20 minutes of exercise, and significantly drops 15-20 minutes after stopping exercise. In addition, when exercise intensity is kept below ~60% maximal oxygen uptake (VO_{2max}), high-energy phosphate depletion is minimal (Karlsson *et al*, 1971). Resynthesis of phosphocreatine stores to baseline happens within about 5 minutes after stopping exercise (Dawson *et al*, 1997). It appears that an ideal warm-up for short-term performance would include exercise at <60% VO_{2max} for 10-20 minutes, with the recovery between warm-up and exercise at least 5 minutes and no more than 20 minutes (Bishop, 2003b).

Intermediate (>10 seconds, but <5 minutes) and long-term (≥5 minutes) exercise performance has been shown to improve most when warm-up increases VO_2 above baseline but minimizes fatigue (Bishop, 2003b). A warm-up intensity of about 70% VO_{2max} appears to be optimal for moderately trained athletes (Stewart and Sleivert, 1998; Bishop *et al*, 2001). However, for untrained individuals the optimal warm-up intensity may be slightly lower (Bruyn-Prevost and Lefebvre, 1980). Ozyener *et al* (2001) have shown that VO_2 reaches steady state with 5-10 minutes of moderate to heavy intensity warm-up and returns to near baseline within 5 minutes of recovery. This is consistent with previous reports that exercise performance is enhanced with warming-up at 60-80%

VO_{2max} for ≥10 minutes (Franks, 1983). However, multiple studies have shown no improvement in intermediate and long-term performance when recovery between warm-up and exercise is ≥5 minutes (Grodjinovsky and Magel, 1970; Bruyn-Prevost and Lefebvre, 1980; Andzel, 1982; Genovely and Stamford, 1982).

Most studies have shown that warm-up improves short-term, intermediate, and long-term performance. However, several studies have shown no improvement or decreased performance with warm-up prior to short-term (Margaria *et al*, 1971; Sargeant and Dolan, 1987; Hawley *et al*, 1989), intermediate (Bruyn-Prevost and Lefebvre, 1980; Genovely and Stamford, 1982) and long-term performance (Grodjinovsky and Magel, 1970; Andzel, 1978; Gregson *et al*, 2002a). In many of these studies, the lack of improvement in performance can be attributed to the warm-up being low intensity (Andzel, 1982; Bruyn-Prevost and Lefebvre, 1980; Genovely and Stamford, 1982), depleting glycogen stores (Bergstrom *et al*, 1967), increasing thermoregulatory strain (Kozlowski *et al*, 1985), and/or the recovery period lasting too long (Bruyn-Prevost and Lefebvre, 1980; Genovely and Stamford, 1982).

Most of the research on the effect of active warm-up on performance has been conducted on athletes or apparently healthy populations. There are no known studies looking at the effect of an active warm-up on exercise performance in patients with PAD, nor on 6MWT performance in any population.

Passive Warm-Up

Passive warm-up generally refers to passively increasing T_m or core temperature (T_c) prior to exercise or athletic performance. In studies comparing active warm-up to passive warm-up, exercise performance is enhanced to a greater extent with active warm-up (Dolan *et al*, 1985; O'Brien *et al*, 1997). This would suggest that improved performance with warm-up includes other factors in addition to increased temperature, such as elevated baseline VO_2 (Andzel, 1982), residual metabolic acidemia (Gerbina *et al*, 1996), increased neuromuscular post-activation potentiation (Gullich and Schmidtbleicher, 1996; Young *et al*, 1998), and possible psychological influences (Massey *et al*, 1961). However, as early as 1945, most of the performance improvements associated with warm-up have been attributed to temperature-related mechanisms (Asmussen and Boje, 1945). Since then, research using passive warm-up has largely been used to elucidate temperature versus non-temperature effects on performance.

The effect of elevating T_m on short-term exercise performance depends on the type of exercise performed. The results of a few small studies have shown that increasing T_m above baseline appears to have little (Bergh *et al*, 1979) or no (Davies and Young, 1983) effect on maximal isometric force. However, T_m improves dynamic force (Davies and Young, 1983) and maximal power as much as 5% per ^{o}C increase in T_m (Binkhorst *et al*, 1977). In addition, fast-twitch fibers appear to have a greater thermal dependance for maximal force velocity than slow-twitch fibers (Bennett, 1984). It has also been suggested that passive heating may be important in short-term performance to keep T_m elevated between active warm-up and performance (Bishop, 2003a).

Early research has observed that passive warm-up appears to have a beneficial effect on intermediate performance. Asmussen and Boje (1945) reported in two subjects that a hot shower for 10 minutes at $47^{o}C$ raised both T_m and $T_{c,}$ and improved work performance lasting 4-5 minutes. Other researchers have also reported that passive heating increases T_m and T_c, and subsequently, improves intermediate duration performance (Muido, 1946; Carlile, 1956). Increases in T_c may be more important than increases in T_m for intermediate performance. When T_m was allowed to return to baseline, but T_c remained elevated, performance remained improved (Muido, 1946). In a more recent study, passive warm-up that increased T_m improved cycle performance at 120 rpms but not at 60 rpms (Ferguson *et al*, 2002). This would suggest that the specificity of the task, or the rate of muscle contraction, may be a factor in whether passive warm-up improves intermediate performance.

Passive warm-up may have a neutral or negative impact on long-term performance due to impaired thermoregulation (Fortney *et al*, 1984; Nadel, 1987). In addition, other studies have shown a decrease in muscle endurance performance with passive heating (Clarke *et al*, 1958; Edwards *et al*, 1972; Kozlowski *et al*, 1985). More recent research has shown passive heating prior to exercise impaired intermittent (Gregson *et al*, 2002a) and continuous (Gregson *et al*, 2002b) run times to exhaustion when T_c was elevated to 38°C. In fact, the opposite has shown to have a beneficial effect. It has been demonstrated that cooling prior to endurance performance increases run time to exhaustion in trained runners (Lee and Haymes, 1995). Overall, it appears that passive warm-up may be detrimental to long-term performance.

The effects of passive heating on cardiovascular health and function, and on exercise performance in clinical populations, including patients with PAD, will be discussed in the next two sections.

PASSIVE HEAT AND CARDIOVASCULAR HEALTH AND FUNCTION

The benefits of including walking exercise as the primary mode of treatment for patients with PAD are well established (Gerhard-Herman *et al*, 2017; Hamburg and

Balady, 2011; Askew *et al*, 2014). Generally, any walking will improve patient outcomes, but supervised exercise therapy is superior to unsupervised exercise therapy (Fokkenrood *et al*, 2013). However, compliance is low and dropout rates are high with these types of exercise programs because patients are either unwilling or unable to tolerate the exercise due to the symptoms of claudication pain (Bendermacher *et al*, 2007). Finding alternative treatments for patients with PAD is critical to improve patient outcomes such as reduced cardiovascular events and mortality. Passive heat therapy has shown promise in improving cardiovascular health and function and may prove to be an important strategy in the treatment of patients with PAD.

Historical Perspective

Recent attention has been focused on the use of passive heat therapy to improve cardiovascular health and function. The impetus for this attention can be attributed to the results of a 30-year prospective study out of Finland showing that a lifetime of sauna use could reduce the risk of both cardiovascular-related and all-cause mortality (Laukkanen *et al*, 2015). Known as the Finnish Kuopio Ischemic Heart Disease Risk Factor Study, investigators recruited 2315 middle-aged men from the city and surrounding area of Kuopio in Eastern Finland. The subjects were assigned to groups based on both frequency and duration of sauna use. The risk of sudden cardiac death was significantly lower in subjects who used sauna baths 4-7 days per week compared to subjects who only used sauna baths once per week (10.1% vs 5.0%, respectively). Similarly, sauna sessions lasting >19 minutes conferred significant reduction in all-cause mortality risk compared to sessions less than 11 minutes (30.8% vs. 49.1%, respectively). The mechanisms underlying the cardioprotective effects of sauna use were not measured in this study so a direct cause and effect could not be made. Also, the investigators recognize a couple of limitation to the study. First, the frequency and duration of sauna use was determined during a baseline questionnaire in the mid-late 1980's and sauna usage may have changed due to changes in health or other factors before the end of the data collection period at death or 2011, whichever occurred first. Second, only men were recruited for this study and future research including women is needed to extrapolate the results to a large population. Regardless, the associative data between sauna use and health outcomes in a large population study is extremely promising.

This landmark study was built on previous work by others studying sauna use in Finland. In 1966, Dr. Hasan, Dr. Karvonen (exercise science pioneer, well-known for his target heart rate formula) and Dr. Piironen published a review on the physiological effects of extreme heat using Finnish sauna baths (Hasan *et al*, 1966). In this paper, the authors discuss the historical use of saunas in Finland and the purported statements of the health benefits with sauna use. The authors neither supported nor refuted these health claims but mentioned that more research was needed to show evidence of cause and effect. This review did show direct physiological evidence that sauna use increased sweat rate, cardiac output, and heart rate to similar levels seen with mild intensity exercise. Even at that time, the authors also were keenly aware that finding a control group would be difficult due to the prevalence of sauna bath use in Finnish culture.

Cardiovascular Health

This earlier work has been followed-up by others investigating the cardiovascular benefits and changes with Finnish sauna use. Moderate temperature sauna bathing (approximately 80 degrees C) can increase heart rate to 100 beats/min and improve blood pressure and left ventricle function similar to that shown with regular exercise (Luurila, 1992; Hannuksela and Ellahham, 2001). Higher temperature sauna bathing (90-100 degrees C) can elicit heart rates up to 150 beats/min, along with corresponding increases in plasma norepinephrine, growth hormone, and testosterone (Kukkonen-Harjula, *et al*, 1989). Also, skin blood flow and sweat rate increase as sauna temperature increases with a secretion rate as high as 1.0 kg/hour with sauna temperatures of 90 degrees C (Vuori, 1988). Additionally, a recent epidemiological study has shown reductions in cardiovascular deaths and all-cause mortality in the general Finnish male population with the combined effect of sauna use and high cardiorespiratory fitness (Kunutsor *et al*, 2018).

In a recent review article of the cardiovascular and other health benefits of sauna bathing, the authors of the Finnish Kuopio Study recognize that there are different forms of passive heat therapy, such as hot water immersion, infrared sauna, and Waon therapy, but that their review would focus “only on the evidence from the traditional Finnish saunas because they are the most widely studied to date” (Laukkanen *et al*, 2018). They then proceed to cite the results of multiple studies using other forms of heat therapy, stating that there is a “biological plausibility” that the same outcomes seen in the other forms of heat therapy will be seen with the Finnish sauna baths. From here forward, for the sake of consistency and to include the results from studies using different forms of heat therapy, the term passive heat therapy will be used for the multiple approaches of delivering heat stress.

Microvascular Function

The literature on passive heat therapy is only recently beginning to include studies investigating the microvascular and macrovascular mechanisms leading to the cardiovascular and other health benefits seen in these previous studies. Microvascular impairment, often referred to as endothelial dysfunction, precedes the sequelae of events leading to inflammation and plaque formation in cardiovascular disease (Verma *et al*, 2003). Endothelial function can be directly measured by endovascular ultrasound but this is expensive, invasive, and impractical for multiple measurements over time. Since endothelial dysfunction has been shown to be a systemic process that occurs similarly in the microvasculature throughout the body (Sax *et al*, 1987), noninvasive measurements in systemic vessels can identify individuals who have (Anderson *et al*, 1995) or who are at risk of developing (IJzerman *et al*, 2003) coronary artery or peripheral arterial disease.

A frequently used noninvasive assessment of endothelial function is flow-mediated dilatation (FMD), a technique introduced by Celermajer and colleagues (Celermajer *et al*, 1992). It has been shown that nitric oxide (NO) synthesized and released from the endothelium is largely responsible for flow-dependent dilation of the microvasculature (Joannides *et al*, 1995) and measurement of arterial dilation and blood flow after a period occlusive ischemia can be an indirect assessment of endothelial function. Drs. Thijssen, Green, and other colleagues using FMD in their research have developed recommendations on the use of FMD in clinical trials (Thijssen *et al*, 2011). After a period of quiet rest, subjects should be placed in a supine position with the imaged artery at or near the heart level. Baseline artery diameter and blood velocity should be measured using duplex ultrasound for at least 1 minute prior to cuff inflation.

The cuff should be placed below the imaged artery and inflated for 5 minutes, since longer inflation times could elicit vasodilation from other mechanisms besides NO (Mullen *et al*, 2001). Post-deflation measurements should start before the cuff is released and be continuous for $\geq$3 minutes in upper limb arteries and $\geq$5 minutes in lower limb arteries. When reporting data, use peak blood velocity, report FMD in both absolute (mm) and relative change (%), and report the shear-rate stimulus (Thijssen *et al*, 2011). These guidelines will help ensure the accuracy and consistency of the reported data across different laboratories and solidify the prognostic value of FMD as a clinical tool for predicting future risk.

Although FMD has been used in many clinical trials across many patient populations (Inaba *et al*, 2010), there are few studies measuring FMD in trials using passive heat therapy. In 2001, Imamura and colleagues used a form of sauna treatment known as Waon therapy using 60 degrees C far-infrared sauna bath in patients with coronary risk factors. They showed that 15 minutes of sauna followed by 30 minutes of warming in bed daily for 2 weeks improved endothelial function by FMD (Imamura *et al*, 2001). Even though the sauna treatment used far-infrared, the 60 degrees C temperature was significantly lower than the 80-100 degrees C seen in the Finnish sauna studies yet still showed significant vascular improvement. The next year, the same group of researchers used the same protocol to study patients with chronic heart failure. They showed improvement in endothelial function by FMD, which they suggested led to improved cardiac function as measured by a decrease in plasma levels of brain natriuretic peptide (Kihara *et al*, 2002). Of note, both studies showed significant microvascular improvement with only two weeks of therapy. This work was followed-up by Ohori and colleagues, again using Waon therapy on patients with chronic heart failure. Although, the protocol was slightly different in that the treatments occurred 5 times per week for 3 weeks. Again, this treatment was effective in increasing endothelial function in patients with chronic heart failure as measured by FMD. However, this time the increase in FMD was significantly and positively associated with increases in both 6-minute walk test distance and with peak oxygen uptake (Ohori *et al*, 2012). Carter and colleagues used direct lower-body heating to measure the vascular effects on the upper-body (Carter *et al*, 2014). They showed that lower-limb heating at 40 degrees C, done 3 times per week for 8 weeks, improved FMD midway through the study. However, FMD returned to baseline at 8 weeks. Even though the FMD was not significantly different at the end of the study, the change at 4 weeks established this as the first study to show systemic benefits with local passive heating (Carter *et al*, 2014).

More recently, Brunt and colleagues conducted the first study to comprehensively measure both microvascular and macrovascular changes with repeated bouts of whole-body passive heat therapy using hot water immersion (Brunt *et al*, 2016a). The sedentary, yet otherwise young and healthy, subjects in this study were immersed at shoulder-level in a hot tub set a 40.5 degrees C for nearly 30 minutes until rectal temperature reached 38.5 degrees C, at which time the subjects sat in the hot tub at waist-level and maintained rectal temperature for 60 minutes. In addition to macrovascular improvements such as reductions in arterial stiffness, wall thickness and blood pressure, this study also showed significant and meaningful improvements in endothelial function as measured by FMD (Brunt *et al*, 2016a). In a separate study during the same timeframe, Brunt and colleagues published the first study exploring the mechanisms behind the improvements seen in microvascular function with passive heat therapy (Brunt *et al*, 2016b). Using a similar heating protocol, they also locally heated the foreman and used microdialysis fibers to deliver either a control solution, a NO synthase inhibitor (to block NO production), or a superoxide dismutase inhibitor (to block the effect of oxidative stress or inflammation). They demonstrated that the improvement in endothelial function with passive heat therapy was due to improved NO-dependent dilation (Brunt *et al*, 2016b).

It appears that improvement in endothelial function may require repeated bouts of heat therapy. Thomas and colleagues compared an acute about of exercise (30-min treadmill running at 65-75% predicted maximal heart rate) to an acute bout of passive heat therapy (30-min seated at waist-level in water at 42 degrees C) in ten young and healthy subjects in a cross-over design. Shear rate in the superficial femoral artery increased in both groups with a greater increase during immersion. However, FMD remained unchanged during both interventions (Thomas *et al*, 2016). It may also be that a time course is necessary for endothelial adaptations to occur.

Macrovascular Function

The literature on the assessment of macrovascular function with passive heat therapy is even more anemic than that for microvascular function. Macrovascular dysfunction, specifically arterial stiffness of the elastic arteries such as the aorta, is highly predictive of cardiovascular risk (Vlachopoulos *et al*, 2010). The most common technique for quantifying arterial stiffness is measurement of the pulse wave velocity (PWV) between the carotid and the femoral arteries (central or cfPWV) or between the carotid and the brachial arteries (peripheral or cbPWV). The PWV is calculated as the distance between the two arteries divided by the time difference between the pulses of each artery (in m/s). Although both central and peripheral PWV measurements can assess arterial stiffness, the cfPWV is considered the gold standard because it directly measures the stiffness of the aorta and is more associated with risk of cardiovascular events than the peripheral PWV (Mitchell *et al*, 2010).

Ganio, Crandall, and colleagues were the first to show that an acute bout of passive heat stress can reduce arterial stiffness as measured by both peripheral and central PWV (Ganio *et al*, 2011). Eight healthy subjects were placed supine and dressed in full-body water perfused suits heated to 49 degrees C. PWVs were measured when core temperature reached 0.5, 1.0 and 1.5 degrees C above baseline. When analyzed as group means, neither central nor peripheral PWVs significantly changed from baseline at any of the time points. However, there was a significant correlation between baseline central and peripheral PWVs and the percent change. Individuals with the highest resting PWV had the largest reduction in PWV with passive heating (Ganio *et al*, 2011). As previously mentioned, the comprehensive study by Brunt and colleagues also showed a reduction in arterial stiffness (Brunt *et al*, 2016a). In addition to measuring central PWV, the authors assessed arterial stiffness using measurements of carotid and femoral artery diameter and pulse pressures to calculate dynamic arterial stiffness and the beta-stiffness index. Also decreases in superficial femoral artery wall thickness, mean and diastolic blood pressure were demonstrated. The only other known study to show improved arterial stiffness with passive heat therapy was a recently published non-randomized study by the Finnish Kuopio Study researchers using Finnish sauna bathing. One hundred-two asymptomatic subjects with at least one cardiovascular risk factor received an acute bout of dry sauna bath (30-min at 73 degrees C). Mean PWV decreased after sauna use and continued to remain below baseline 30 minutes into recovery (Lee *et al*, 2018).

PASSIVE HEAT AND PERIPHERAL ARTERIAL DISEASE

The mechanisms underlying the cardiovascular and other health benefits of passive heat therapy are just now on the verge of discovery. In addition to the cardioprotective benefits to the apparently healthy population, many patient populations with cardiovascular disease may gain even greater benefit from passive heat therapy. Patients with peripheral arterial disease (PAD) often have extremely low functional capacities due to severe disease and/or significant flow limitations and leg pain with walking (intermittent claudication). Claudication pain with minimal activity can limit or discourage these patients from participating in exercise that could improve their health outcomes or quality of life. The 10-year mortality rate for patients with PAD is over 60% for men and 33% for women (Criqui *et al*, 1992).

Clinical Outcomes

There are a few published trials that have investigated passive heat interventions on patients with peripheral arterial disease. In 2007, Tei and colleagues published a research correspondence to the editor of the *Journal of the American College of Cardiology* purporting that the Waon therapy they developed years earlier for patients with heart failure was now showing benefits for patients with PAD (Tei *et al*, 2007). In this study they used Waon therapy as described previously, this time 5 days per week for 10 weeks on 20 patients with PAD and an ankle-brachial pressure index (ABI) of <0.9. The results showed that resting leg pain decreased, walking distance increased, and 7 pre-existing ulcers healed or significantly improved. Also, the ABI increased in almost every subject, which is remarkable since this is typically not expected with exercise training (Parmenter *et al*, 2010; Harwood *et al*, 2016). A few years later, this same research group showed that 6 weeks of Waon therapy increased the mobilization of CD34+ cells in patients with PAD (Shinsato *et al,* 2010). Increased CD34+ cells. Characterized as endothelial progenitor cells, have been associated with improved vascular function and health. In one study, patients with PAD and critical limb ischemia avoided recommended amputation after injection of CD34+ cells (Subrammaniyan *et al*, 2011).

Vascular Function

Studies investigating the cardiovascular responses to passive heat therapy on patients with PAD so far have only assessed acute bouts of heat therapy. Neff and colleagues used water-perfused pants at 48 degrees C for 90 minutes on sixteen patients with PAD (Neff *et al*, 2016). They demonstrated increases in popliteal artery peak blood flow velocity, average blood flow velocity, and a doubling of the average blood flow compared to baseline. In addition, circulating levels of the vasoconstrictor endothelin-1 concentrations decreased and both mean systolic and mean diastolic blood pressure dropped 11mmHg and 6 mmHg, respectively (Neff *et al*, 2016). In the most recent study, Thomas and colleagues used lower-limb hot-water immersion to elicit cardiovascular changes in 11 patients with PAD and 10 controls (Thomas *et al*, 2017). Subjects were submersed at waist-level in hot water at 42.1 ± 0.6 degrees C for 30 minutes. The PAD group also performed a treadmill test for 3 minutes at 3 km/h at 10% grade. Shear rate increased in the popliteal (local) and brachial (systemic) arteries in both the PAD and control groups. In the PAD group, antegrade shear increased and retrograde shear decreased. The shear patterns in the PAD group during heat therapy was similar the shear patterns observed during exercise, without the claudication that was reported during exercise. Both central and peripheral PWV was reduced in both groups after heat therapy. Another significant finding was the large drop in mean arterial blood pressure of approximately 22 mmHg, which continued to remain below baseline 3 hours after the intervention. (Thomas *et al*, 2017).

Acute Heating and Exercise Performance

Recent studies have shown that acute bouts of passive heating can improve exercise performance in patients with PAD. Pellinger *et al* (2019) studied six patients with PAD under three randomized treatments conditions 2-7 days apart: bilateral lower leg heating for either 15 or 45 minutes, or control. Six-minute walk test distance increased 10% and 12% after 15- and 45-minute bouts of heating, respectively, compared to the control condition. Both improvements were clinically significant. In addition, popliteal artery blood flow increased under both heating conditions (Pellinger *et al*, 2019). More recently, Monroe *et al* (2021) randomized 16 patients with PAD in a crossover design to 90 minutes of lower-extremity heating or a sham treatment prior to a cardiopulmonary exercise test on a treadmill. Peak treadmill walking time improved in the heat therapy condition, but claudication onset time did not improve (Monroe *et al*, 2021).

Chronic Heating and Exercise Performance

The literature on the effects of chronic passive heat therapy on patients with PAD is small but gaining interest among researchers. Shinsato and colleagues (2010), in the same study that demonstrated improvements in ABI and CD34+ cells with Waon therapy, also showed a remarkable improvement in 6MWT distance of 81 m with only six weeks of Waon therapy in patients with PAD. Akerman *et al* (2019) compared 12-weeks of heat therapy versus supervised exercise in patients with PAD. The heat therapy group used whole-body water immersion at 39 degrees C, 3-5 days/week for ≤30 minutes, followed by ≤30 minutes of calisthenics. The exercise group walked or engaged in other modes of exercise for ≤90 minutes 1-2 days/week. Both groups showed a 41 m improvement in 6MWT distance, improvement in 6MWT pain-free walking distance, as well as decreases in resting blood pressure. There was no significant difference between groups in any of those three outcome measures (Akerman *et al*, 2019). Monroe *et al* (2020) studied the effect of 6 weeks of bilateral leg heat therapy with water-perfused trousers at 48 degrees C versus a sham treatment on 6MWT distance in patients with PAD. There was no difference between groups in the 6MWT distance; however, the heat therapy group reported a perceived improvement in physical function by scoring significantly higher than the sham group on the 'physical function' subscale of the 36-item Short Form Health Survey (Monroe *et al*, 2020). Monroe and colleagues (2022) have more recently published a study looking at the effects of home-based lower-extremity heat therapy on walking performance in patients with PAD. Patients with claudication were randomized into leg heat therapy or sham. Patients in both groups were given water-perfusion trousers and a portable pump and were instructed to use the treatment for 90 minutes daily for 8 weeks. At the 8-week follow-up, the heat therapy group increased an average of 21 m in the 6MWT distance while the sham group showed no improvement. The benefits of passive heating on walking performance in patients with PAD will become clearer as the literature grows in this area.

CHAPTER III

METHODS

GENERAL EXPERIMENTAL APPROACH

All studies in this dissertation were approved by the Institutional Review Board of PeaceHealth (Project #1582624-7) and were conducted on patients enrolled in the vascular rehabilitation program in the Cardiovascular Wellness and Rehabilitation department at the Oregon Heart & Vascular Institute at PeaceHealth Sacred Heart Medical Center RiverBend in Springfield, Oregon. Written informed consent was obtained from all subjects after a verbal briefing of all experimental procedures for a given study.

The study detailed in chapter IV (Training Study) compared outcomes of two different exercise training protocols on patients with PAD enrolled in a vascular rehabilitation program. Patient were randomly assigned to follow either a novel combination treadmill and ambulation training protocol or a standard treadmill only training protocol for a minimum of 20 sessions within 12 weeks. A 6MWT was conducted on each patient prior to and after the respective training programs. In addition, a quality-of-life questionnaire (SF-36) was administered before and after completing the study. A physical activity enjoyment scale questionnaire (PACES) was administered at the end of the program.

The study detailed in chapter V (Acute Study) investigated the effect of an active warm-up on the 6MWT in patients with PAD enrolled in a vascular rehabilitation program. Subjects were randomized to either warm-up by walking on a treadmill for 10-

12 minutes or not warm-up prior to conducting a 6MWT. Subjects returned to conduct a second 6MWT 2-3 days later under the opposite condition as the first test.

Chapter VI is a review article on novel training techniques for patients with PAD. The article includes a literature review showing improved outcomes with exercise in patients with PAD, the state of the practice of PAD rehabilitation (SET for PAD), an introduction to overground walking in the supervised clinical setting, a discussion of the effects of an active warm-up on exercise performance, beginning the narrative on the benefits of passive heating in the rehabilitative setting, and directions for future research.

SUBJECT CHARACTERIZATION

Twenty-three (15 males, 8 females) total patients participating in vascular rehabilitation enrolled in either the training study, acute study or both studies detailed in this dissertation. Fourteen subjects (8 males, 6 females) completed the training study detailed in chapter IV (Table 3.1). Sixteen subjects (10 males, 6 females) completed the acute study detailed in chapter V (Table 3.2). Twenty-one subjects originally enrolled in the training study but 7 withdrew from or were unable to complete the study due to medical reasons including three subjects with back and other orthopedic issues, one patient with pulmonary issues, one patient with neurological issues, one patient with angina, and one patient did not return after the initial visit.

Table 3.1 Training Study Subject Characteristics

	COMBO	STAND	*p* value
Age, y	74.4 (2.1)	82.5 (6.6)	$p < 0.028$*
Sex, M/F	5/3	3/3	
Height, cm	170.6 (6.6)	162.6 (9.5)	$p = 0.121$
Weight, kg	79.7 (22.3)	74.9 (19.4)	$p = 0.676$
Body mass index, kg/m^2	27.1 (6.1)	28.0 (5.1)	$p = 0.765$
Ankle-brachial index	0.67 (0.16)	0.62 (0.16)	$p = 0.635$
Tibial-brachial index	0.46 (-)	0.60 (-)	
Systolic blood pressure, mmHg	140.3 (12.0)	142.7 (18.2)	$p = 0.785$
Diastolic blood pressure, mmHg	70.8 (9.7)	73.7 (10.4)	$p = 0.604$
Mean arterial pressure, mmHg	93.9 (7.5)	96.7 (10.4)	$p = 0.597$
Diabetes, y/n	3/5	2/4	
Insulin, y/n	1/7	1/5	
Tobacco, y/n	1/7	0/6	

Values are mean (SD), ankle-brachial index and tibial-brachial index are from leg with worst disease. * $p < 0.05$.

Table 3.2 Acute Study Subject Characteristics

Age, y	77.3 (5.3)
Sex, M/F	10/6
Height, cm	169.6 (8.3)
Weight, kg	78.8 (16.2)
Body mass index, kg/m^2	27.3 (4.6)
Ankle-brachial index	0.68 (0.15)
Tibial-brachial index	0.31 (0.22)
Systolic blood pressure, mmHg	135.5 (17.5)
Diastolic blood pressure, mmHg	70.8 (9.2)
Mean arterial pressure, mmHg	91.9 (9.5)
Diabetes, y/n	8/8
Insulin, y/n	2/14
Tobacco, y/n	1/15

Values are mean (SD), ankle-brachial index and tibial-brachial index are from leg with worst disease.

SIX-MINUTE WALK TEST

The primary outcome measurement in the training study in chapter VI and the acute study in chapter V is the six-minute walk test (6MWT). In patients with PAD, both 6MWT distance and treadmill walking time are associated with risk of cardiovascular events and mortality in patients with PAD (McDermott *et al*, 2008b; Olin, 2008; de Liefde *et al*, 2009; de Liefde, 2010; Schiano *et al*, 2006). Hiatt *et al* (2014) presented a case that the treadmill is a better functional test than the 6MWT for patients with PAD; however, McDermott *et al* (2014) argue that the 6MWT should be the preferred method of measuring functional improvement in patients with PAD. The 6MWT is more closely associated with daily physical activity levels than the treadmill test (McDermott *et al*, 2008c), and is also more sensitive to changes in functional mobility and decline (McDermott *et al*, 2011). Additionally, there is very little day-to-day variability or learning effect with repeated 6MWT. Montgomery and Gardner (1998), Gardner *et al* (2001) and McDermott *et al* (2008b) have all shown no learning effect with repeated 6MWT in patients with PAD.

The American Thoracic Society (ATS) published a statement in 2002 on guidelines for conducting a 6MWT (ATS, 2002). This statement continues to be the standard today. The studies in chapter IV and chapter V followed the ATS guidelines for conducting the 6MWT. Prior to performing each 6MWT, patients rested in a seated position for at least 10 minutes near the start while researchers measured baseline heart rate, blood pressure, and oxygen saturation. The 6MWT course was conducted in a hallway with turnaround points marked with cones set 100 ft apart. If needed, patients used their usual walking aids, such as canes and walkers, during the test.

Each patient was instructed to walk as far as possible for 6 minutes without running and was permitted to slow down or stop if experiencing symptoms of claudication or dyspnea, and to inform the researchers at the onset of symptoms. Patients who needed to stop were instructed to remain standing, leaning on a wall if necessary, and then resume walking when able. Researchers let the patients know the time at the end of each minute, gave a warning with 15 seconds remaining that the test was nearing the end, and then gave the command to stop when 6 minutes were completed. The time and distance were marked at the point of claudication onset and the final distance was marked where the patient stopped at the completion of 6 minutes.

At the end of 6 minutes, patients were instructed to sit in a nearby chair while researchers collected immediate-post heart rate, blood pressure, oxygen saturation, and asked patients for subjective ratings of effort and pain using Borg, claudication, dyspnea, and angina scales. After the patient had recovered for at least 5 minutes, researchers measured recovery heart rate, blood pressure and oxygen saturation, and confirmed that any symptoms had resolved prior to the patient leaving. Researchers measured and recorded the distances at the claudication onset point and at the completion of the 6MWT. Distances were measured in feet and converted to meters for reporting.

TRAINING STUDY PROTOCOLS

The study in chapter IV was a prospective, randomized, controlled trial. The study randomized patients with symptomatic peripheral arterial disease into one of two different training protocols: a combination treadmill plus ambulation protocol (COMBO) or a standard treadmill protocol (STAND). All participants began with baseline measurements including a six-minute walk test, and completion of the SF-36 quality of life questionnaire. After baseline measurements, participants were randomly assigned after stratification by sex and six-minute walk test (above vs. below 350 m) to ensure equal numbers of males and females and an equal distribution of higher and lower performers to each group.

The training intervention included between 20-36 exercise visits of SET for PAD within a 12-week period using either the COMBO or the STAND training protocol.

Within two weeks of completing the training intervention, each participant began the follow-up measurements including repeating a six-minute walk test, completion of the SF-36 quality of life questionnaire and completion of the Physical Activity Enjoyment Scale (PACES).

Combination Protocol

The COMBO protocol used in the study in chapter IV was a novel protocol designed by the primary investigator to include an extensive warm-up period on the treadmill prior to engaging in the ambulation training on the ground and to take advantage of the specific benefits of overground walking during training.

The warm-up period was extended to 10-20 minutes of total treadmill walking time (versus standard practice of 5-minute warm-ups), began between 1.0-2.0 mph and focused on gradually increasing the workload over the entire warm-up period (versus sudden jumps in workload often seen in warm-up routines). The warm-up included rest periods as needed and continued until 10-20 minutes of walking were accumulated.

After the warm-up period, the training included up to three separate 3 to 10-minute intervals of overground walking until reaching a moderate level of claudication pain. The ambulation training was conducted on an indoor 310-foot walking track. During both the warm-up and the training period, vital signs were measured, and subjective scales of effort and pain were assessed. The goal was to aim for a total walking time of 20-45 minutes between both the warm-up on the treadmill and the ambulation overground.

The cool-down period included 2-5 minutes of gentle ambling and a full body stretching routine if the patient could tolerate that activity. Contrary to the STAND protocol, increases in training intensity often occurred during the current training session if tolerated. Fig.3.1 outlines the training for the COMBO protocol.

Combination Protocol Outline

Warm-up (TREADMILL)

- Accumulate 10-20 minutes on the treadmill
- Start slow (~1.0-1.2mph)
- Gradually increase workload over the first 10-12 minutes (i.e., 0.1mph/1-2 min)
- Rest as needed

Intervals (TRACK)

- Aim for 3 sets of 3-10 minutes walking on the track
- Accumulate up to 30 minutes walking on the track
- Rest as needed

Figure 3.1 Combination Protocol Training Outline

Standard Protocol

The STAND protocol used in the study in chapter IV was the standard treadmill training protocol promoted in the PAD Exercise Training Toolkit developed by the

American Association of Cardiovascular and Pulmonary Rehabilitation and the Vascular Disease Foundation (AACVPR/VDF, 2010).

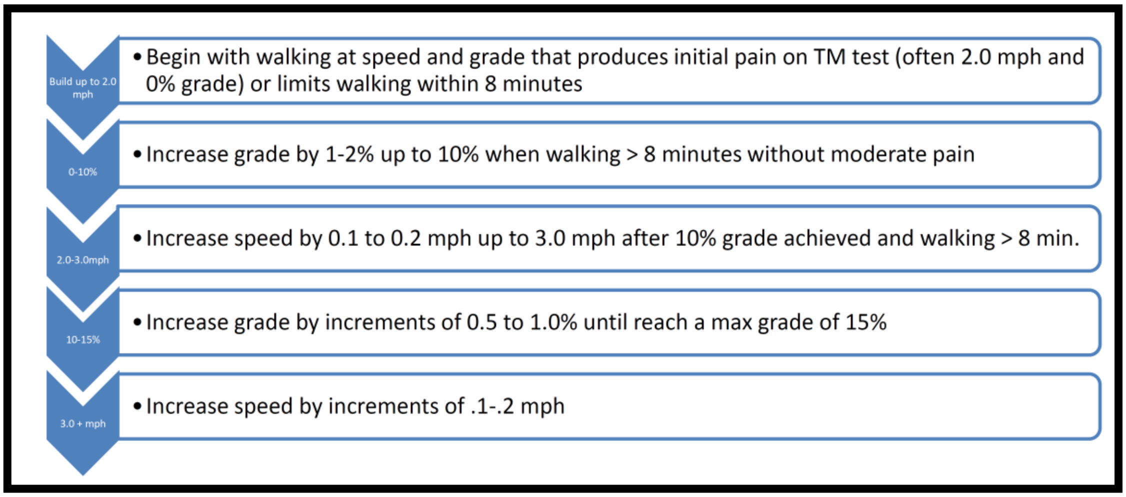
The warm-up period began with a series of ankle and calf exercises and stretches. Patients performed foot taps (with plantarflexion and dorsiflexion) in a seated position for 30 seconds on each foot. Next patients performed a static calf stretch with bent knee for 30 seconds and straight knee for 30 seconds on each calf. The warm-up period continued into the treadmill protocol with patients beginning at 1.0 mph and gradually increasing speed and grade to prescribed intensity within 3-5 minutes. The goal was to aim for a 60-minute exercise session which includes rest periods, a 5-minute warm-up period and a 5-minute cool-down period.

The cool-down period consisted of gradually decreasing the treadmill speed and grade to 1.0 mph and 0% incline within 5 minutes. Contrary to the COMBO protocol, increases in training intensity did not occur during the current training session. Fig.3.2 outlines the training for the STAND protocol.

Standard Protocol Outline

Warm-up: Foot taps (plantar/dorsiflexion) in seated position for 30 seconds. Static calf stretch with bent and straight knee for 30 seconds. Begin treadmill walking at 1.0 mph and gradually increase speed and grade to prescribed intensity within 3-5 minutes.

Aim for 60-minute exercise session which includes rest periods, 5-minute warm-up period and 5-minute cool-down period.



Cool-down: Gradually decrease speed and grade to 1.0 mph and 0% grade within 5 minutes.

Increases in training intensity should occur at the following session and not during the current session.

Figure 3.2 Standard Protocol Training Outline. Adapted from Ehrman *et al*, 2017.

ACUTE STUDY PROTOCOL

The study in chapter V was a prospective, randomized, crossover, controlled trial. The study measured the effect of an active walking warm-up on the 6MWT in patients with symptomatic peripheral arterial disease. All participants completed two 6MWTs 2-3 days apart. After stratification by sex, each subject was block randomized to complete the first 6MWT either following an active walking warm-up or with no warm-up. The second

6MWT was conducted under the opposite condition as the first 6MWT. The warm-up consisted of 10-12 minutes total of walking on a treadmill at a comfortable pace (1.0-1.2 mph for most patients). Under the warm-up condition, patients rested in a seated position for 10 minutes prior to beginning the warm-up. After the completing the warm-up, patients again rested in a seated position for 10 minutes prior to beginning the 6MWT.

During the 6MWTs, total distance walked, claudication onset distance and claudication onset time were measured. The two 6MWTs were conducted during the first two sessions of SET for PAD. After completing the acute study, subjects either participated in the training study if eligible or continued in SET for PAD but were not enrolled in the training study.

HEMODYNAMIC AND OTHER MEASUREMENTS

In the studies detailed in chapters IV and V, heart rate, arterial blood pressure, and pulse oxygen saturation (SpO2) were measured prior to beginning exercise, at the peak workload of exercise and after recovery from exercise as part of standard practice. Heart rate and arterial blood pressure at rest during the initial visit were used to calculate mean arterial pressure, which was reported as a subject characteristic. Metabolic equivalents of task (METs) were calculated from treadmill and/or ground walking speed and grade and used to quantify workload during the training sessions as a secondary outcome. The body mass index (BMI) was calculated from the height and weight at the initial visit and reported as a subject characteristic.

Heart Rate

Heart rate was measured using a three-lead, telemetry electrocardiograph (VersaCare Client Manager, ScottCare, Cleveland, OH, USA) during the initial exercise visit on all subjects and on subsequent visits on select subjects with a history of arrhythmias. Heart rate was measured on all other visits using a pulse oximeter (Nellcor by Covidien/Medtronic, Minneapolis, MN, USA; Masimo, Irvine, CA, USA) and expressed as beats per minute.

Arterial Blood Pressure

Arterial blood pressure was measured in the brachial artery of the arm with the highest pressure using a manual sphygmomanometer and stethoscope. Mean arterial pressure (MAP) was calculated using eq. 3.1, expressed as mmHg, and reported as a subject characteristic.

$$MAP = [(2 \times Diastolic\ BP) + Systolic\ BP] / 3$$

Equation 3.1 Mean Arterial Pressure

Pulse Oxygen Saturation (SpO_2)

Pulse oxygen saturation (SpO2) was measured with pulse oximetry (Nellcor by Covidien/Medtronic, Minneapolis, MN, USA; Masimo, Irvine, CA, USA), using a finger probe and expressed a percentage.

Metabolic Equivalents of Task (METs)

Metabolic Equivalents of Task were calculated using eq. 3.2 from treadmill and/or ground walking speed (m/min) and grade (%) and used to quantify workload during the 6MWTs and the peak of each exercise training session.

$$METs = [(0.1 \times speed) + (1.8 \times speed \times grade) + 3.5] / 3.5$$

Equation 3.2 Metabolic Equivalent of Task

Body Mass Index (BMI)

Body Mass Index (BMI) was calculated from the height and weight at the initial visit, expressed as kg/m^2, and reported as a subject characteristic.

$$BMI = [Weight\ (lbs.) / Height\ (in^2)] \times 703$$

Equation 3.3 Body Mass Index

SUBJECTIVE SCALES OF EFFORT AND PAIN

In the studies detailed in chapters IV and V, subjective measures of effort and pain were assessed at the peak of exercise using standardized scales of perceived effort, claudication, dyspnea, and angina. The Borg Rate of Perceived Exertion (RPE) and claudication level were reported for all subjects. The dyspnea and angina levels were reported only on the subjects who experienced those symptoms.

Borg Rate of Perceived Exertion (RPE) Scale

The 6-20 Borg RPE scale was used to quantify each patient's subjective rating of how hard they felt they were working from "very, very light" to "very, very hard" during the peak of exercise.

Claudication Scale

The 1-5 claudication scale was used to quantify each patient's subjective rating of claudication discomfort at the peak of exercise. The highest rating claudication was also recorded, regardless of the workload. In addition, the time at claudication onset was recorded during the 6MWTs and during each exercise training session.

Dyspnea Scale

The 0-4 dyspnea scale was used to quantify each patient's subjective rating of dyspnea at the peak of exercise. Not all patients experienced symptoms of dyspnea during the study.

Angina Scale

The 0-4 angina scale was used to quantify each patient's subjective rating of angina at the peak of exercise. Most patients did not experience symptoms of angina during the study.

SUBJECTIVE QUESTIONNAIRES

In the study detailed in chapter V, subjective questionnaires were used to compare potential differences in quality-of-life and enjoyment of exercise between subjects in the COMBO and STAND protocols using the *Medical Outcomes Study 36-item short-form health survey* (SF-36) and *Physical Activity Enjoyment Scale* (PACES), respectively.

36-Item Short Form Questionnaire (SF-36)

The SF-36 is a tool designed to measure both physical and mental health outcomes in many scenarios including clinical practice, research, and the general population (Ware and Sherbourne, 1992). The SF-36 assesses eight health concepts including bodily pain, general mental health, vitality, perceived general health, and limitations in physical activities, social activities, and usual activities due to physical or emotional problems.

The SF-36 has been recommended as a quality-of-life measure in the assessment of patients with vascular disease (Beattie *et al*, 1997). Recently, the SF-36 has been used to assess quality-of-life in patients with PAD receiving passive heat therapy compared to an exercise group (Monroe *et al*, 2020) and to a control group (Akerman *et al*, 2019).

Subjects in the study in chapter IV were given the SF-36 questionnaire at both the beginning and the completion of the study to compare quality-of-life differences between subjects in the COMBO and the STAND protocols. See Appendix for a sample of the SF-36 questionnaire.

Physical Activity Enjoyment Scale Questionnaire (PACES)

The health benefits of physical activity are well established, yet most of the general population falls short of meeting national physical activity guidelines (ACSM, 2022). Patients with symptomatic PAD may be even less inclined to participate in activities that cause pain. The COMBO Protocol was designed with in intent of including a gentler and more progressive warm-up than the STAND protocol before reaching the peak workload, potentially increasing enjoyment, and ultimately, participation of the activity. It has been shown that enjoyment of an activity is positively linked with the motivation to perform that activity (Wankel, 1993).

The most commonly used tool to measure enjoyment of physical activity is the PACES questionnaire (Kendzierski and DeCarlo, 1991). The original 18-item PACES was created and validated on a college-age population (Kendzierski and DeCarlo, 1991. A shorter version of PACES was validated and found reliable in older adults (Mullen *et al*, 2011). More recently, this tool was found to be a reliable and invariant assessment tool in adults with functional limitations (Murdock *et al*, 2016). The 18-item PACES questionnaire askes respondents “how you feel *at the moment* about the physical activity you have been doing” using a 7-point bipolar scale, with eleven of the items reverse scored. The higher the score, the greater the enjoyment of the activity (Kendzierski and DeCarlo, 1991).

Subjects in the study in chapter IV were given the PACES questionnaire at the completion of the study to compare physical activity enjoyment differences between subjects in the COMBO and the STAND protocols. See Appendix for a sample of the PACES questionnaire.

CHAPTER IV

TRAINING STUDY: A NOVEL AMBULATION TRAINING PROTOCOL FOR PATIENTS WITH PERIPHERAL ARTERIAL DISEASE

INTRODUCTION

Peripheral arterial disease (PAD) is atherosclerosis of the arteries outside of the heart and brain, particularly the lower extremities, and represents an advanced burden of cardiovascular disease. Patients with PAD have a high risk of morbidity and mortality. The risk of stroke, myocardial infarction (Agnelli *et al*, 2020) and mortality (Hirsch *et al*, 2008) is equivalent to or greater than the risk in patients with coronary artery disease. In addition to a high risk of cardiovascular events, PAD leads to an accelerated decline in physical function and increased disability in both symptomatic and asymptomatic patients (McDermott *et al*, 2002; Gardner *et al*, 2007; McDermott *et al*, 2008a).

For symptomatic patients, the greatest limitation to activity is ischemic pain in the legs known as intermittent claudication. It is estimated that only 10-15% of patients with PAD experience classical claudication symptoms (Hirsch *et al*, 2001; McDermott *et al*, 2001), yet asymptomatic patients show the same decline in functional status and have the same risk of morbidity and mortality as symptomatic patients (Gardner *et al*, 2008).

The first line of treatment for patients with PAD, and without critical limb ischemia, is exercise and risk factor modification. Evidenced-based exercise guidelines for patients with PAD recommend weight-bearing exercise, specifically walking in a supervised setting (Parmenter *et al*, 2011). To guide the clinician in treating patients with PAD, the American College of Sports Medicine has published guidelines for prescribing exercise to patients with PAD (ACSM, 2022). In addition, the American Association of

Cardiovascular and Pulmonary Rehabilitation and Vascular Disease Foundation developed a PAD Exercise Training Toolkit. The toolkit outlines and suggests using a standard treadmill training protocol (AACVPR/VDF, 2010). Both guidelines suggest the treadmill as the preferred mode of exercise for patients with PAD.

Patients with PAD who participate in supervised treadmill exercise programs show greater increases in maximal treadmill walking distance versus patients who participate in unsupervised home-based walking programs or who receive walking advice (Hageman *et al*, 2018). McDermott *et al* (2009) have demonstrated that patients with PAD show large improvements in maximal treadmill walking time (51%) when participating in supervised treadmill exercise interventions, yet only show minimal improvement (6.4%) in 6MWT distances. Conversely, patients with PAD who completed a home-based over ground walking program have shown an improvement (12%) in six-minute walk test distances nearly double that shown in the treadmill training program (McDermott *et al*, 2013). This suggests there may be a specificity of the training mode such that patients who train on a treadmill show greater increases in treadmill performance measures and patients who train overground show greater improvement in the 6MWT distance.

Functional assessment tools, such as the six-minute walk test (6MWT), and treadmill walking time, are associated with risk of cardiovascular events and mortality in patients with PAD (McDermott *et al*, 2008b; Olin, 2008; de Liefde *et al*, 2009; de Liefde, 2010; Schiano *et al*, 2006). The six-minute walk test is more closely associated with daily physical activity levels than the treadmill test (McDermott *et al*, 2008c), and is also more sensitive to changes in functional mobility and decline (McDermott *et al*, 2011). Patients with PAD respond well to exercise training with clinically meaningful improvement in 6MWT distance. An improvement of 30m is clinically meaningful (Gardner *et al*, 2018). This suggests that interventions that increase functional capacity, specifically 6MWT distance, can decrease mortality and improve health outcomes in patients with PAD.

Treadmill only training protocols are beneficial but may not be the optimal training protocol to show increases in 6MWT distance for patients with PAD and intermittent claudication. The treadmill protocol in the PAD Exercise Training Toolkit (AACVPR/VDF, 2010) includes a short warm-up period of 4-5 minutes and then introduces a training workload that is at or near the ischemic (claudication) threshold. The limited warm-up period and sudden intensity in workload has the potential to compromise performance, increase symptoms, and decrease both compliance to and enjoyment of the exercise. In addition, this protocol focuses on increasing treadmill incline (up to 10% or more) over increasing walking speed. The rationale is that patients with PAD generally walk at slow speeds due to their claudication symptoms and would tolerate a change in incline over a change in speed. Using treadmill only walking and including elevation changes not seen in normal daily life may not translate as well to ground walking or to everyday functional capacity.

An ideal exercise training protocol for a patient with PAD would include supervision, an extended warm-up period, progressive increases in workload and overground walking at speeds that mimic normal walking gait. The few studies that have reported the results of supervised ambulation training in the literature have included other modes of exercise in addition to supervised walking (Fahkry *et al*, 2012). Only one randomized controlled trial has included supervised walking as the exclusive mode of training but did not show any treadmill walking performance versus a control group (Gelin *et al*, 2001). Including ambulation training in a supervised setting for patients with PAD may have the potential to improve 6MWT test distance and meaningful clinical outcomes to a greater extent than treadmill training alone.

The purpose of this study was to compare a novel combination treadmill and ambulation training protocol (COMBO) with a commonly used standard treadmill only training protocol (STAND) in patients with PAD. It was hypothesized that the COMBO protocol would prove to be as good or superior to the STAND protocol when measuring the 6MWT distance in patients with PAD.

METHODS

Approval and Informed Consent

This study was approved by the Institutional Review Board of PeaceHealth (Project #1582624-7) and was conducted on patients enrolled the vascular rehabilitation program in the Cardiovascular Wellness and Rehabilitation department at the Oregon Heart & Vascular Institute at PeaceHealth Sacred Heart Medical Center RiverBend in Springfield, Oregon. Written informed consent was obtained from all subjects after a verbal briefing of all experimental procedures.

Subject Characteristics

Fourteen patients (8 males, 6 females) with PAD and symptomatic claudication participated in this study. Inclusion criteria included an ankle-brachial index of less than 0.90 or toe-ankle index of less than 0.80, aged 50-80 years old, a body mass index of less than 40kg/m^2, and free of severe walking limitations. Exclusion criteria included uncontrolled diabetes, unhealed diabetic skin ulcers, unstable angina, and recent myocardial infarction. See table 4.1 for subject characteristics.

Table 4.1 Subject Characteristics

	COMBO	STAND	*p* value
Age, y	74.4 (2.1)	82.5 (6.6)	$p < 0.028$*
Sex, M/F	5/3	3/3	
Height, cm	170.6 (6.6)	162.6 (9.5)	$p = 0.121$
Weight, kg	79.7 (22.3)	74.9 (19.4)	$p = 0.676$
Body mass index, kg/m^2	27.1 (6.1)	28.0 (5.1)	$p = 0.765$
Ankle-brachial index	0.67 (0.16)	0.62 (0.16)	$p = 0.635$
Tibial-brachial index	0.46 (-)	0.60 (-)	
Systolic blood pressure, mmHg	140.3 (12.0)	142.7 (18.2)	$p = 0.785$
Diastolic blood pressure, mmHg	70.8 (9.7)	73.7 (10.4)	$p = 0.604$
Mean arterial pressure, mmHg	93.9 (7.5)	96.7 (10.4)	$p = 0.597$
Diabetes, y/n	3/5	2/4	
Insulin, y/n	1/7	1/5	
Tobacco, y/n	1/7	0/6	

Values are mean (SD), ankle-brachial index and tibial-brachial index are from leg with worst disease. * $p < 0.05$.

Study Protocol

This study was a prospective, randomized, controlled trial comparing a novel training protocol with a commonly used standard treadmill training protocol on patients with PAD. The study randomized patients with symptomatic peripheral arterial disease into one of two different training protocols: a combination treadmill plus ambulation protocol (COMBO) or a standard treadmill protocol (STAND). All participants began with baseline measurements including a six-minute walk test, and completion of the SF-36 quality of life questionnaire. After baseline measurements, participants were randomly assigned after stratification by sex and six-minute walk test (above vs. below 350 m) to ensure equal numbers of males and females and an equal distribution of higher and lower performers to each group.

The training intervention included between 20-36 exercise visits of SET for PAD within a 12-week period using either the COMBO or the STAND training protocol.

Within two weeks of completing the training intervention, each participant began the follow-up measurements including repeating a six-minute walk test, completion of the SF-36 quality of life questionnaire and completion of the Physical Activity Enjoyment Scale (PACES).

Combination Protocol

The COMBO protocol used in this study was a novel protocol designed by the primary investigator to include an extensive warm-up period on the treadmill prior to engaging in the ambulation training on the ground and to take advantage of the specific benefits of overground walking during training.

The warm-up period was extended to 10-20 minutes of total treadmill walking time (versus standard practice of 5-minute warm-ups), began between 1.0-2.0 mph and focused on gradually increasing the workload over the entire warm-up period (versus sudden jumps in workload often seen in warm-up routines). The warm-up included rest periods as needed and continued until 10-20 minutes of walking were accumulated.

After the warm-up period, the training included up to three separate 3 to 10-minute intervals of overground walking until reaching a moderate level of claudication pain. The ambulation training was conducted on an indoor 310-foot walking track. During both the warm-up and the training period, vital signs were measured, and subjective scales of effort and pain were assessed. The goal was to aim for a total walking time of 20-45 minutes between both the warm-up on the treadmill and the ambulation overground.

The cool-down period included 2-5 minutes of gentle ambling and a full body stretching routine if the patient could tolerate that activity. Contrary to the STAND protocol, increases in training intensity often occurred during the current training session if tolerated. Fig.4.1 outlines the training for the COMBO protocol.

Combination Protocol Outline

Warm-up (TREADMILL)
- Accumulate 10-20 minutes on the treadmill
- Start slow (~1.0-1.2mph)
- Gradually increase workload over the first 10-12 minutes (i.e., 0.1mph/1-2 min)
- Rest as needed

Intervals (TRACK)
- Aim for 3 sets of 3-10 minutes walking on the track
- Accumulate up to 30 minutes walking on the track
- Rest as needed

Figure 4.1 Combination Protocol Training Outline

Standard Protocol

The STAND protocol used in this study was the standard treadmill training protocol promoted in the PAD Exercise Training Toolkit developed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Vascular Disease Foundation (AACVPR/VDF, 2010).

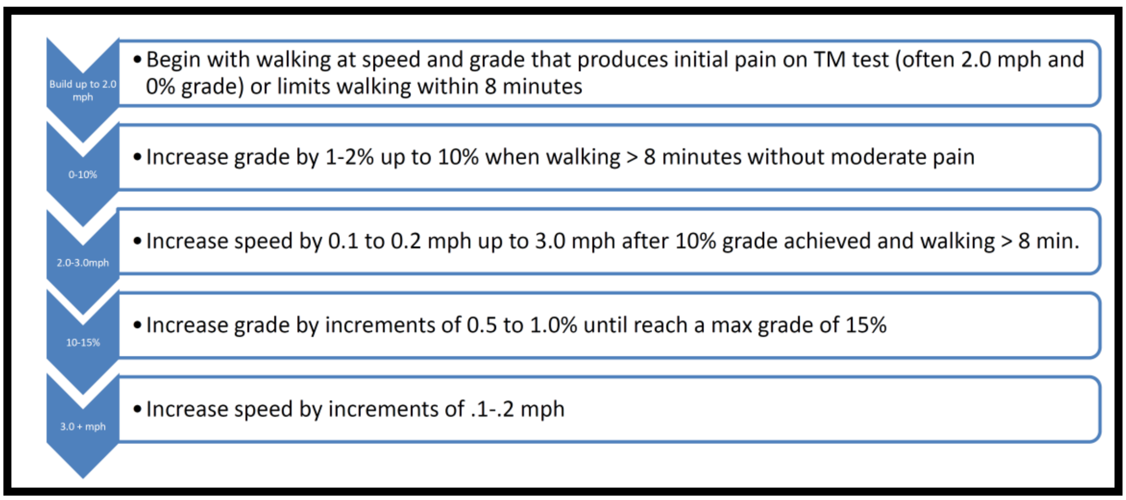
The warm-up period began with a series of ankle and calf exercises and stretches. Patients performed foot taps (with plantarflexion and dorsiflexion) in a seated position for

30 seconds on each foot. Next patients performed a static calf stretch with bent knee for 30 seconds and straight knee for 30 seconds on each calf. The warm-up period continued into the treadmill protocol with patients beginning at 1.0 mph and gradually increasing speed and grade to prescribed intensity within 3-5 minutes. The goal was to aim for a 60-minute exercise session which includes rest periods, a 5-minute warm-up period and a 5-minute cool-down period.

Standard Protocol Outline

Warm-up: Foot taps (plantar/dorsiflexion) in seated position for 30 seconds. Static calf stretch with bent and straight knee for 30 seconds. Begin treadmill walking at 1.0 mph and gradually increase speed and grade to prescribed intensity within 3-5 minutes.

Aim for 60-minute exercise session which includes rest periods, 5-minute warm-up period and 5-minute cool-down period.



Cool-down: Gradually decrease speed and grade to 1.0 mph and 0% grade within 5 minutes.

Increases in training intensity should occur at the following session and not during the current session.

Figure 4.2 Standard Protocol Training Outline. Adapted from Ehrman *et al*, 2017.

The cool-down period consisted of gradually decreasing the treadmill speed and grade to 1.0 mph and 0% incline within 5 minutes. Contrary to the COMBO protocol, increases in training intensity did not occur during the current training session. Fig.4.2 outlines the training for the STAND protocol.

Six-Minute Walk Test

The 6MWT was conducted following American Thoracic Society guidelines (ATS, 2002). The 6MWT course was conducted in a hallway with turnaround points marked with cones set 100 ft apart. If needed, patients used their usual walking aids, such as canes and walkers, during the test.

Hemodynamic and Other Measurements

Heart rate and blood pressure. Heart rate was measured using either a three-lead, telemetry electrocardiograph (VersaCare Client Manager, ScottCare, Cleveland, OH, USA) or a pulse oximeter (Nellcor by Covidien/Medtronic, Minneapolis, MN, USA; Masimo, Irvine, CA, USA) and expressed as beats per minute. Arterial blood pressure was measured in the brachial artery of the arm with the highest pressure using a manual sphygmomanometer and stethoscope.

Pulse Oxygen Saturation. Pulse oxygen saturation (SpO_2) was measured with pulse oximetry (Nellcor by Covidien/Medtronic, Minneapolis, MN, USA; Masimo, Irvine, CA, USA), using a finger probe and expressed a percentage.

Subjective Scales of Effort and Pain. Subjective measures of effort and pain were assessed at the peak of effort or pain using standardized scales of perceived effort, claudication, dyspnea, and angina. The Borg 6-20 Rate of Perceived Exertion (RPE) and claudication level (1-5 scale) were reported for all subjects. Subjects were also assessed for dyspnea (0-4 scale) and angina (0-4 scale

Statistical Analyses

The primary outcome in this study was to show a clinically significant difference in 6MWT distance between the COMBO and the STAND protocols in patients with PAD. To achieve the necessary power for significance (power at 80%, alpha of 0.05), this study needed to enroll a minimum of 13 subjects in each of the COMBO and the STAND groups, for a total of at least 26 subjects. An unpaired t-test was used for all comparisons. Data are reported as means and 95% confidence intervals unless otherwise noted.

RESULTS

Fourteen patients (8 males, 6 females) with PAD and symptomatic claudication participated in this study. Subject characteristics are shown in Table 4.1. Eight (8) patients were randomized into the COMBO protocol and 6 patients into the STAND protocol. Exercise training showed significant and clinically meaningful improvement in 6MWT total walking distance (44±8 m, p=0.0002) regardless of group. However, improvement in total walking distance did not differ between the two protocols (COMBO 54±7 m vs STAND 32±15 m, p=0.192). The comparison of improvement in 6MWT total walking distance between the COMBO and STAND training protocols is presented in Figure 4.3.

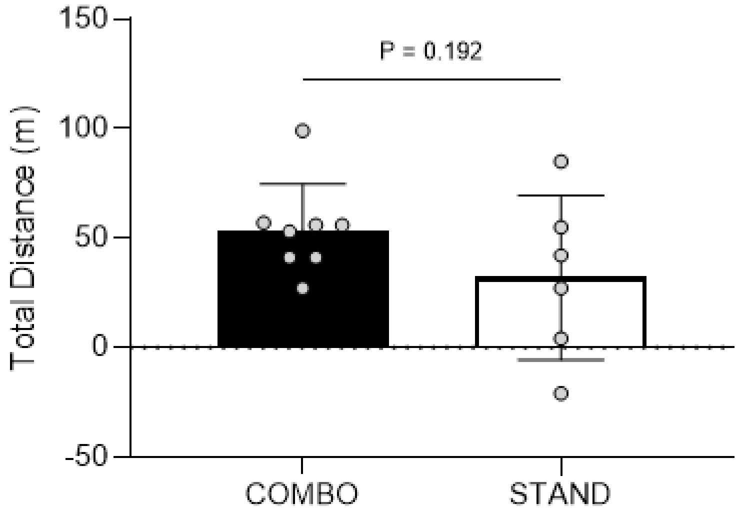


Figure 4.3 The comparison of improvement in six-minute walk test total distance between the COMBO (54±7 m) and STAND (32±15 m) training protocols in patients with PAD; *n* = 14 (COMBO-8, STAND-6); *p* value is an unpaired t-test between conditions.

The comparison of 6MWT claudication onset distance between the COMBO and STAND training protocols is presented in Figure 4.4. Patients in the COMBO training group showed a greater improvement in claudication onset distance compared to patients in the STAND training group (COMBO 79±24 m vs STAND -7±20 m, *p*=0.030).

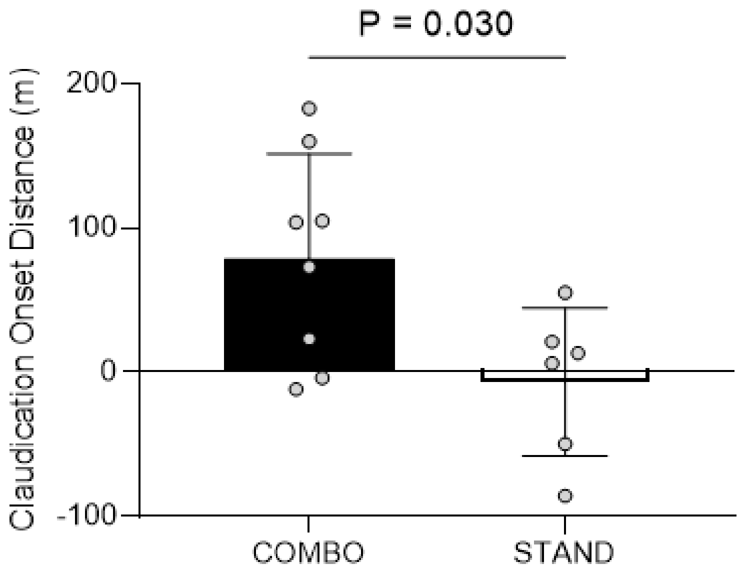


Figure 4.4 The comparison of six-minute walk test claudication onset distance between the COMBO (79±24 m) and STAND (-7±20 m) training protocols in patients with PAD; *n* = 14 (COMBO-8, STAND-6); *p* value is an unpaired t-test between conditions.

The comparison of 6MWT claudication onset time between the COMBO and STAND training protocols is presented in Figure 4.5. Patients in the COMBO training group showed a greater improvement in claudication onset time compared to patients in the STAND training group (COMBO 49±20 s vs STAND -32±23 s, *p*=0.028).

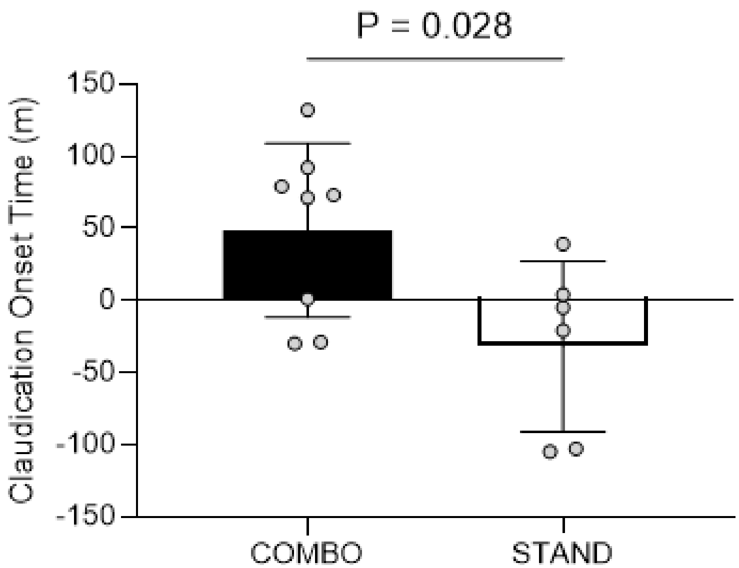


Figure 4.5 The comparison of six-minute walk test claudication onset time between the COMBO (49±20 s) and STAND (-32±23 s) training protocols in patients with PAD; *n* = 14 (COMBO-8, STAND-6); *p* value is an unpaired t-test between conditions.

During the exercise training sessions, the peak clinical measurements of heart rate, blood pressure, pulse oxygen saturation, claudication pain level, and rate of perceived exertion did not differ between groups. In addition, peak workload and number of training sessions was not different between groups. The COMBO training group exercised longer than the STAND training group. See table 4.2 for results of the peak measurements during the exercise training sessions.

Table 4.2 Peak Clinical Measurements During the Training Sessions

	COMBO	STAND	*p* value
Heart rate, bpm	109.8±7.2	108.8±4.4	$p = 0.920$
Systolic blood pressure, mmHg	171.0±6.2	175.0±7.1	$p = 0.694$
Diastolic blood pressure, mmHg	85.5±3.6	85.3±2.8	$p = 0.972$
Pulse oxygen saturation, %	93.5±1.4	92.7±1.4	$p = 0.626$
Claudication (1-5 scale)	3.9±0.3	3.3±0.5	$p = 0.373$
Rate of perceived exertion (6-20 scale)	13.6±0.4	14.3±0.5	$p = 0.635$
Peak workload, METs	3.2±0.1	2.9±0.5	$p = 0.546$
Peak training minutes	29.4±2.8	19.1±1.1	$p < 0.009$*
Number of training sessions	26.6±0.9	25.3±1.9	$p = 0.581$

Values are mean (±95% CI); * $p < 0.05$; *p* values are unpaired t-tests between conditions.

The was no change in the SF-36 Physical (2.3±1.4, $p = 0.123$) or Mental (2.3±1.4, $p = 0.123$) composite scores pre and post, regardless of training group, and there was no difference between groups. Also, there was no difference in the PACES scores between training groups at the end of the study. See table 4.3 for a comparison of the results of the SF-36 and PACES questionnaires between the COMBO and STAND groups.

Table 4.3 Subjective Questionnaires

	COMBO	STAND	*p* value
SF-36 Physical Delta	0.6±1.8	4.5±1.9	$p = 0.189$
SF-36 Mental Delta	0.8±3.0	-2.2±1.9	$p = 0.453$
PACES Score	91.0±9.2	104.0±4.0	$p = 0.137$

Values are mean (±95% CI); *p* values are unpaired t-tests between conditions.

DISCUSSION

The purpose of this study was to compare a novel combination treadmill and ambulation training protocol (COMBO) with a commonly used standard treadmill only training protocol (STAND) in patients with PAD. The results of this study did not support our primary hypothesis that the COMBO training protocol would improve

6MWT distance compared to the STAND training protocol in patients with PAD. However, the results of this study did support our secondary hypotheses that the COMBO training protocol would improve 6MWT claudication onset distance and claudication onset time compared to the STAND training protocol in patients with PAD.

The peak cardiovascular responses, claudication pain level, and perceived exertion level were the same between training groups. Also, the number of training sessions and the peak exercise intensity were consistent between with the COMBO and STAND training groups. However, patients in the COMBO training group were able to exercise for about 10 minutes longer at the peak of exercise compared to the STAND training group. It is unclear why the COMBO group exercised longer than the STAND group but patients in both training groups were progressed based on how they tolerated the previous session and based on patient feedback of when they wanted to end each session. It was noted that some patients in this study preferred overground walking versus treadmill walking and may have felt motivated to exercise for a longer duration.

Patient perception of physical or mental quality-of-life did not improve with either the COMBO or STAND training protocols. Additionally, patient enjoyment of physical activity did not differ between groups. A quality-of-life questionnaire (SF-36) given pre and post study and an enjoyment of physical activity questionnaire (PACES) given at the end of the study did not differ between the COMBO training group and the STAND training group.

There are some limitations to this study. First, cardiopulmonary gas exchange, vascular function, and core temperature were not measured. It is unknown how these variables were influenced by or differed with each training protocol. These measurements could reveal the effectiveness of the treadmill warm-up in the COMBO protocol. Second, exercise training duration was not controlled between groups. The patients in the COMBO protocol exercise for a longer duration than the patients in the STAND protocol, which may have contributed to the improved performance. Finally, the study was not powered for significance.

Future studies are needed to identify optimal exercise training protocols that can maximize functional capacity in patients with PAD. It has been demonstrated that patients with PAD who train on the treadmill show large improvements in treadmill walking performance (McDermott *et al*, 2009) and patients who participate in home-based overground walking programs show larger improvements in 6MWT distance (McDermott *et al*, 2013) than studies in which patients train exclusively on the treadmill. The current study showed that ambulation training improved 6MWT claudication onset distance and claudication onset time compared to a treadmill only training protocol. There appears to be a benefit to including ambulation training as part of the exercise protocol for patients with PAD. Optimizing an ambulation training protocol could be explored in future research by enrolling larger numbers of patients and by modifying components of the exercise prescription, such as the duration or intensity of the workload.

CONCLUSION

The current study compared a novel combination treadmill and ambulation training protocol (COMBO) with a commonly used standard treadmill only training protocol (STAND) in patients with PAD. This was the first study to compare the difference between two training protocols on 6MWT performance in patients with PAD.

The 6MWT total distance did not differ between the COMBO and STAND training protocols. However, both the 6MWT claudication onset distance and claudication onset time were greater in the COMBO group versus the STAND group. The results of this study suggest that ambulation training may improve 6MWT performance compared treadmill only training in patients with PAD. Enrolling more patients and modifying the duration and intensity of the exercise prescription may affect the results in future studies.

CHAPTER V

ACUTE STUDY: ACTIVE WARM-UP AND SIX-MINUTE WALK TEST DISTANCE IN PATIENTS WITH PERIPHERAL ARTERIAL DISEASE

INTRODUCTION

Peripheral arterial disease (PAD) is atherosclerosis of the arteries outside of the heart and brain, particularly the lower extremities, and represents an advanced burden of cardiovascular disease. Patients with PAD have a high risk of morbidity and mortality. The risk of stroke, myocardial infarction (Agnelli *et al*, 2020) and mortality (Hirsch *et al*, 2008) is equivalent to or greater than the risk in patients with coronary artery disease. In addition to a high risk of cardiovascular events, PAD leads to an accelerated decline in physical function and increased disability in both symptomatic and asymptomatic patients (McDermott *et al*, 2002; Gardner *et al*, 2007; McDermott *et al*, 2008a).

The first line of treatment for patients with PAD, and without critical limb ischemia, is exercise and risk factor modification. Evidenced-based exercise guidelines for patients with PAD recommend weight-bearing exercise, specifically walking in a supervised setting (Parmenter *et al*, 2011). Improving exercise performance in patients with PAD is important to offset the decreased physical activity levels seen in this population, which strongly predicts a high all-cause mortality risk (Garg *et al*, 2006; Gardner *et al* 2008).

Functional assessment tools, such as the six-minute walk test (6MWT) and treadmill walking time, are associated with risk of cardiovascular events and mortality in patients with PAD (McDermott *et al*, 2008b; Olin, 2008; de Liefde *et al*, 2009; de Liefde, 2010; Schiano *et al*, 2006). The six-minute walk test is more closely associated with daily physical activity levels than the treadmill test (McDermott *et al*, 2008c), and is also more sensitive to changes in functional mobility and decline (McDermott *et al*, 2011). There is very little day-to-day variability or learning effect with repeated 6MWTs in patients with PAD (Montgomery and Gardner, 1998). Patients with PAD respond well to exercise training with clinically meaningful improvement in 6MWT distance. An improvement of 30m is clinically meaningful (Gardner *et al*, 2018). This suggests that interventions that increase functional capacity, specifically 6MWT distance, can decrease mortality and improve health outcomes in patients with PAD.

Any opportunity to enhance the increase in functional capacity of patients with PAD could significantly improve the health outcomes in this deconditioned population. One potential strategy to optimize the benefit of walking training could be the inclusion of an effective warm-up. Warm-up prior to exercise can be categorized as either active or passive. Recent studies have shown that acute bouts of passive heating can improve exercise performance in patients with PAD. Pellinger *et al* (2019) showed that bilateral lower leg heating increased 6MWT distance in patients with PAD by 10% and 12% after 15- and 45-minute bouts of heating, respectively, compared to controls. Both improvements were clinically significant (Gardner *et al*, 2018). In addition, Monroe *et al* (2021) showed that 90 minutes of lower-extremity heating prior to a cardiopulmonary exercise test on a treadmill improved peak treadmill walking time.

It is unknown how an active warm-up effects the 6MWT distance with any population. An extended warm-up period has the potential to improve the time and workload achieved by patients with PAD during each exercise session, and ultimately, enhance the improvement over the course of a training program. Specifically, an active walking warm-up may improve the results of the 6MWT distance on patients with PAD.

The purpose of this study was to quantify the effect of an active walking warm-up on the results of the 6MWT distance in patients with PAD. It was hypothesized that an active walking warm-up of 10-12 minutes would improve 6MWT distance in patients with PAD.

METHODS

Approval and Informed Consent

This study was approved by the Institutional Review Board of PeaceHealth (Project #1582624-7) and was conducted on patients enrolled in the vascular rehabilitation program in the Cardiovascular Wellness and Rehabilitation department at the Oregon Heart & Vascular Institute at PeaceHealth Sacred Heart Medical Center RiverBend in Springfield, Oregon. Written informed consent was obtained from all subjects after a verbal briefing of all experimental procedures.

Subject Characteristics

Sixteen patients (10 males, 6 females) with PAD and symptomatic claudication participated in this study. Inclusion criteria included an ankle-brachial index of less than 0.90 or toe-ankle index of less than 0.80, aged 50-80 years old, a body mass index of less than 40kg/m^2, and free of severe walking limitations. Exclusion criteria included uncontrolled diabetes, unhealed diabetic skin ulcers, unstable angina, and recent myocardial infarction. See table 5.1 for subject characteristics.

Table 5.1 Subject Characteristics

Age, y	77.3 (5.3)
Sex, M/F	10/6
Height, cm	169.6 (8.3)
Weight, kg	78.8 (16.2)
Body mass index, kg/m^2	27.3 (4.6)
Ankle-brachial index	0.68 (0.15)
Tibial-brachial index	0.31 (0.22)
Systolic blood pressure, mmHg	135.5 (17.5)
Diastolic blood pressure, mmHg	70.8 (9.2)
Mean arterial pressure, mmHg	91.9 (9.5)
Diabetes, y/n	8/8
Insulin, y/n	2/14
Tobacco, y/n	1/15

Values are mean (SD), ankle-brachial index and tibial-brachial index are from leg with worst disease.

Study Protocol

This study was a prospective, randomized crossover, controlled trial measuring the effect of an active walking warm-up on the 6MWT in patients with symptomatic PAD. All participants completed two 6MWTs 2-3 days apart. After stratification by sex, each subject was block randomized to complete the first 6MWT either following an active walking warm-up (WARM-UP) or with no warm-up (NO WARM-UP). The second 6MWT was conducted under the opposite condition as the first 6MWT. The warm-up consisted of 10-12 minutes total of walking on a treadmill at a comfortable pace (1.4-2.1 METs. Under the warm-up condition, patients rested in a seated position for 10 minutes prior to beginning the 6MWT. See figure 5.1 for an outline of the study protocol.

During the 6MWTs, total distance walked, claudication onset distance, and claudication onset time were measured. In addition, heart rate, arterial blood pressure and pulse oxygen saturation (SpO_2) were measured after 10 minutes of resting prior to beginning the 6MWT, in the immediate-post stage of the 6MWT, and after at least 5 minutes of recovery from the 6MWT. Patients were also assessed for subjective levels of perceived exertion, claudication, dyspnea, and angina during the 6MWT.

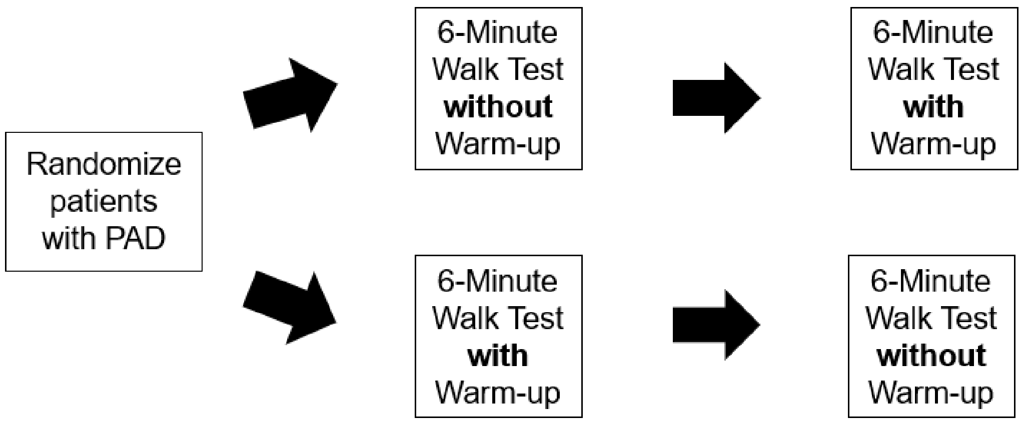


Figure 5.1 Study Protocol

Six-Minute Walk Test

Each 6MWT was conducted following American Thoracic Society guidelines (ATS, 2002). The 6MWT course was conducted in a hallway with turnaround points marked with cones set 100 ft apart. If needed, patients used their usual walking aids, such as canes and walkers, during the test.

Hemodynamic and Other Measurements

Heart rate and blood pressure. Heart rate was measured using either a three-lead, telemetry electrocardiograph (VersaCare Client Manager, ScottCare, Cleveland, OH, USA) or a pulse oximeter (Nellcor by Covidien/Medtronic, Minneapolis, MN, USA; Masimo, Irvine, CA, USA) and expressed as beats per minute. Arterial blood pressure was measured in the brachial artery of the arm with the highest pressure using a manual sphygmomanometer and stethoscope.

Pulse Oxygen Saturation. Pulse oxygen saturation (SpO2) was measured with pulse oximetry (Nellcor by Covidien/Medtronic, Minneapolis, MN, USA; Masimo, Irvine, CA, USA), using a finger probe and expressed a percentage.

Subjective Scales of Effort and Pain. Subjective measures of effort and pain were assessed at the peak of effort or pain using standardized scales of perceived effort, claudication, dyspnea, and angina. The Borg 6-20 Rate of Perceived Exertion (RPE) and claudication level (1-5 scale) were reported for all subjects. Subjects were also assessed for dyspnea (0-4 scale) and angina (0-4 scale).

Statistical Analyses

The primary outcome of this study was to quantify the effect of an active warm-up on the results of the 6MWT test on patients with PAD. To achieve the necessary power for significance (power at 80%, alpha of 0.05), this study needed to enroll a minimum of 11 subjects. A paired t-test was used to compare differences in total 6MWT distance, claudication onset distance, and claudication onset time under the warm-up and no warm-up conditions. Data are reported as means and 95% confidence intervals unless otherwise noted.

RESULTS

Sixteen patients (10 males, 6 females) with PAD and symptomatic claudication participated in this study. Subject characteristics are shown in Table 5.1. The effect of an active warm-up on 6MWT total walking distance are presented in Figure 5.2. Total walking distance did not differ between the two study conditions (WARM-UP 297±17 m vs NO WARM-UP 304±16 m, *p*=0.358).

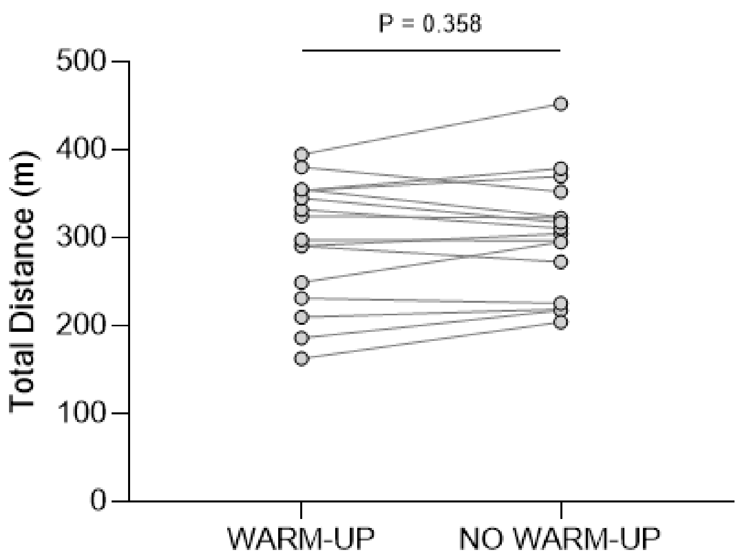


Figure 5.2 The effect of an active warm-up on the six-minute walk test total distance with WARM-UP (297±17 m) and NO WARM-UP (304±16 m) conditions in patients with PAD; *n* = 16 (10M, 6F); *p* value is a paired t-test between conditions.

The effect of an active warm-up on 6MWT claudication onset distance are presented in Figure 5.3. Claudication onset distance did not differ between the two study conditions (WARM-UP 142±24 m vs NO WARM-UP 120±16 m, p=0.188).

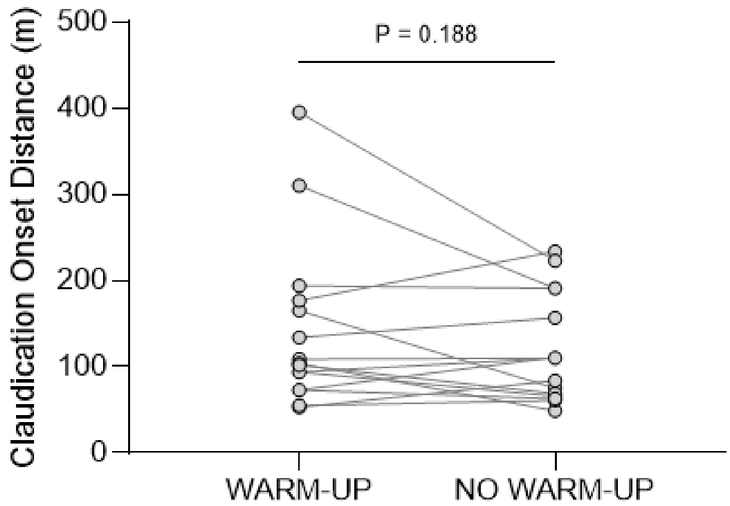


Figure 5.3 The effect of an active warm-up on the six-minute walk test claudication onset distance with WARM-UP (142±24 m) and NO WARM-UP (120±16 m) conditions in patients with PAD; *n* = 16 (10M, 6F); *p* value is a paired t-test between conditions.

The effect of an active warm-up on 6MWT claudication onset time are presented in Figure 5.4. Claudication onset time did not differ between the two study conditions (WARM-UP 154±19 s vs NO WARM-UP 137±16 s, p=0.272).

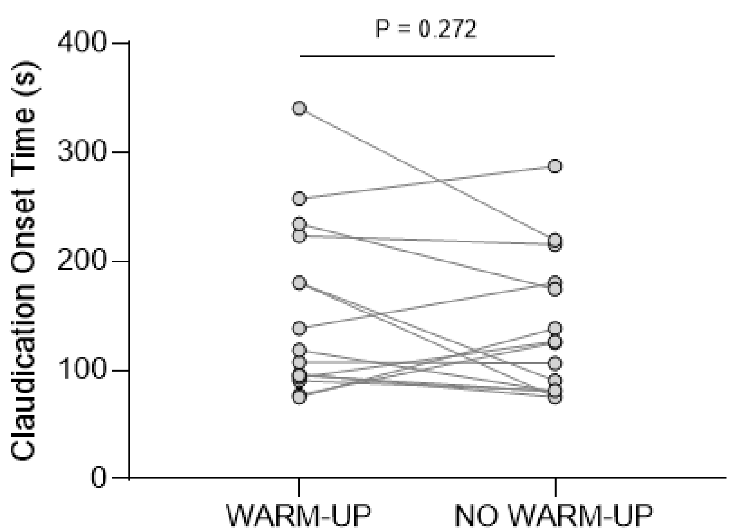


Figure 5.4 The effect of an active warm-up on the six-minute walk test claudication onset time with WARM-UP (154±19 s) and NO WARM-UP (137±16 s) conditions in patients with PAD; *n* = 16 (10M, 6F); *p* value is a paired t-test between conditions.

During each 6MWT, the peak clinical measurements of heart rate, blood pressure, pulse oxygen saturation, claudication pain level, and rate of perceived exertion did not differ between condition. See table 5.2 for results of the peak clinical measurements during the 6MWTs under the NO WARM-UP and the WARM-UP conditions.

Table 5.2 Peak Clinical Measurements During the Six-Minute Walk Tests

	NO WARM-UP	WARM-UP	*p* value
Heart rate, bpm	89.3±2.5	92.1±3.0	$p = 0.421$
Systolic blood pressure, mmHg	159.3±6.3	153.1±6.3	$p = 0.227$
Diastolic blood pressure, mmHg	71.6±2.6	70.0±2.5	$p = 0.854$
Pulse oxygen saturation, %	97.3±0.8	97.4±0.9	$p = 0.792$
Claudication (1-5 scale)	3.2±1.0	3.2±1.1	$p = 0.806$
Rate of perceived exertion (6-10 scale)	12.9±0.4	13.2±0.5	$p = 0.589$

Values are mean (±95% CI); *p* values are paired t-tests between conditions.

Incidentally, there was a significant increase (p=0.047) in total walking distance on the second 6MWT (308±18 m) versus the first 6MWT (294±15 m), regardless of condition.

DISCUSSION

There are no known studies looking at the effect of an active warm-up on exercise performance in patients with PAD, nor on 6MWT performance in any population. The purpose of this study was to quantify the effect of an active walking warm-up on the results of the 6MWT distance in patients with PAD. Previous studies have demonstrated that acute bouts of passive heating can confer clinically significant improvements in 6MWT distance (Pellinger *et al*, 2019) and peak treadmill walking time (Monroe *et al*, 2021). However, it is unknown how an active warm-up effects the 6MWT distance in patients with PAD. The results of this study did not support our primary hypothesis that an active walking warm-up of 10-12 minutes would improve 6MWT distance in patients with PAD. Additionally, the results of this study did not support our secondary hypotheses that an active walking warm-up of 10-12 minutes would improve 6MWT claudication onset distance and claudication onset time in patients with PAD.

The level of intensity and effort appeared consistent between conditions. The peak vital sign measurements of heart rate, blood pressure, and pulse oxygen saturation did not differ between conditions. In addition, reported peak claudication pain level and rate of perceived exertion was similar between conditions.

Further, in an unexpected finding, there was a significant but subclinical increase in total walking distance on the second 6MWT versus the first 6MWT (14±6 m, p=0.047), regardless of condition. This was a modest increase but appears contrary to previous research showing very little day-to-day variability or learning effect with repeated 6MWT in patients with PAD (Montgomery and Gardner, 1998; Gardner *et al*, 2001; McDermott *et al*, 2008b). However, the conditions were not the same each time, so the comparison is not completely equivalent. The difference does reveal potential unknown learning effects that require further investigation and should be considered when designing protocols utilizing the 6MWT in this population.

There are some limitations to this study. First, cardiopulmonary gas exchange, vascular function, and core temperature were not measured. Exercise performance lasting about six minutes in duration has been shown to improve most when warm-up increases VO_2 above baseline but minimizes fatigue (Bishop, 2003b), so it is unknown how the active warm-up in this study affected these variables. Second, since acute passive heating increases exercise performance in patients with PAD (Pellinger *et al*, 2019; Monroe *et al*, 2021) and the active warm-up in this study did not, it is very possible that the warm-up in this study was insufficient in intensity and/or duration to create a stimulus to improve exercise performance. Third, contrary to point number two, the active warm-up in this study may have been too much of a stimulus in some patients and led to increased fatigue prior to the 6MWT. Finally, multiple studies have shown no performance improvement in exercise lasting about six minutes when recovery between warm-up and exercise is longer than 5 minutes (Grodjinovsky and Magel, 1970; Bruyn-Prevost and Lefebvre, 1980; Andzel, 1982; Genovely and Stamford, 1982), however, these studies were not on clinical populations. During the current study, the recovery between warm-up and exercise was 10 minutes in duration to minimize fatigue between bouts of exercise and to allow time for claudication symptoms to resolve.

Future studies are needed to elucidate the ideal warm-up prior to exercise training in patients with PAD. It may be likely that a subset of patients, such as higher functioning patients, may show significant improvement from an active warm-up prior to exercise and other patients, such as lower functioning patients, may benefit from passive heating prior to exercise. This could be explored by measuring core temperature, vascular function, and cardiopulmonary gas exchange during exercise and the recovery periods to quantify the time course of how these measurements might change.

CONCLUSION

The current study was the first to assess the effect of an active warm-up on the 6MWT in patients with PAD. The 6MWT total distance did not differ between the WARM-UP and NO WARM-UP conditions. Additionally, neither the 6MWT claudication onset distance nor claudication onset time differed between the WARM-UP and NO WARM-UP conditions. The results of this study suggest that an active warm-up of 10-12 minutes of walking on a treadmill at a workload between 1.4-2.1 METs may not be enough of a stimulus to increase 6MWT distance in patients with PAD. Modifying the intensity and the recovery periods may affect the results in future studies. Further, learning effects should be considered when designing protocols that utilize the 6MWT.

CHAPTER VI

REVIEW ARTICLE: EXPLORING NOVEL EXERCISE AND TRAINING TECHNIQUES IN PATIENTS WITH PERIPHERAL ARTERIAL DISEASE

INTRODUCTION

Peripheral arterial disease (PAD) is atherosclerosis of the arteries outside of the heart and brain, particularly the lower extremities. Approximately 8.5 million Americans have PAD, including more than 14% of people over 70 years old (Selvin and Erlinger, 2004) and 22% of people over 80 years old (Benjamin *et al*, 2017). This number will continue to grow and become a greater public health burden as the population ages. The major risk factors for PAD are the same as for other cardiovascular diseases with smoking and diabetes being the most potent risk factors (Murabito *et al*, 1997; Benjamin *et al*, 2017).

Peripheral arterial disease represents an advanced burden of cardiovascular disease and patients with PAD have a high risk of morbidity and mortality. The risk of stroke, myocardial infarction (Agnelli *et al*, 2020) and mortality (Hirsch *et al*, 2008) is equivalent to or greater than the risk in patients with coronary artery disease. The 10-year mortality risk for patients with PAD ranges from 22-70% depending on age and severity of risk factors (Criqui *et al*, 1992; Feringa *et al*, 2007).

In addition to a high risk of cardiovascular events, PAD leads to an accelerated decline in physical function and increased disability in both symptomatic and asymptomatic patients (McDermott *et al*, 2002; Gardner *et al*, 2007; McDermott *et al*, 2008a). For symptomatic patients, the greatest limitation to activity is ischemic pain in the legs known as intermittent claudication. It is estimated that only 10-15% of patients with PAD experience classical claudication symptoms (Hirsch *et al*, 2001; McDermott *et al*, 2001), yet asymptomatic patients show the same decline in functional status and have the same risk of morbidity and mortality as symptomatic patients. Regardless of symptoms, PAD contributes to functional decline and increased risk of adverse events in both symptomatic and asymptomatic patients (Gardner *et al*, 2008).

EXERCISE TRAINING AND SIX-MINUTE WALK TEST PERFORMANCE

Improving exercise performance in patients with PAD is important to offset the decreased physical activity levels seen in this population, which strongly predicts a high all-cause mortality risk (Garg *et al*, 2006; Gardner *et al* 2008). Functional assessment tools, such as the six-minute walk test (6MWT) and treadmill walking time, are associated with risk of cardiovascular events and mortality in patients with PAD (McDermott *et al*, 2008b; Olin, 2008; de Liefde *et al*, 2009; de Liefde, 2010; Schiano *et al*, 2006). The six-minute walk test is more closely associated with daily physical activity levels than the treadmill test (McDermott *et al*, 2008c), and is also more sensitive to changes in functional mobility and decline (McDermott *et al*, 2011). There is very little day-to-day variability or learning effect with repeated 6MWT in patients with PAD (Montgomery and Gardner, 1998; Gardner *et al*, 2001; McDermott *et al*, 2008b).

Patients with PAD respond well to exercise training with clinically meaningful improvement in 6MWT distance. An improvement of 30m is clinically meaningful (Gardner *et al*, 2018). McDermott *et al* (2009) showed that 24-weeks of supervised treadmill exercise increased 6MWT distance over 35 m in patients with PAD compared with matched controls. In a population of patients with PAD, McDermott *et al* (2011) have shown that changes in 6MWT distance correlate with clinically meaningful outcomes such as mobility loss and mortality. Patients with the greatest decrease in 6MWT distance had the highest mobility loss, mortality, and cardiovascular disease. These results demonstrate that interventions that increase functional capacity, specifically 6MWT distance, can decrease mortality and improve health outcomes in patients with PAD.

CURRENT PRACTICE OF PAD REHABILITATION

The first line of treatment for patients with PAD, and without critical limb ischemia, is exercise and risk factor modification. Evidenced-based exercise guidelines for patients with PAD recommend weight-bearing exercise, specifically walking in a supervised setting (Parmenter *et al*, 2011). However, until recently, the opportunities for patients with PAD to participate in structured exercise programs were limited to patients who could self-pay or who participated in a research study. In 2017, the Center for Medicare and Medicaid Services (CMS) announced a national coverage determination for Supervised Exercise Therapy (SET) for patients with symptomatic PAD (CMS Decision Memo, 2017). Most SET for PAD services are being provided within cardiac rehabilitation programs due to current infrastructure and staff skill set.

In the six years since CMS began covering SET for PAD, many cardiac rehabilitation programs have incorporated this service into their programs. However, the volumes in most programs remain relatively modest as this service continues to grow and rehabilitation programs develop automatic referral streams from vascular surgeons and interventionalist. To guide the clinician in treating patients with PAD, the American Association of Cardiovascular and Pulmonary Rehabilitation and Vascular Disease Foundation developed a PAD Exercise Training Toolkit. The toolkit outlines and suggests using a standard training protocol of supervised treadmill walking as the primary mode of exercise (AACVPR/VDF, 2010). In addition to the toolkit, the American College of Sports Medicine has published guidelines for prescribing exercise to patients with PAD (ACSM, 2022). Both guidelines suggest using the treadmill as the preferred mode of exercise for patients with PAD. Currently, most patients in SET for PAD programs are using the treadmill as the primary mode of walking training.

OVERGROUND WALKING IN A SUPERVISED CLINICAL SETTING

Multiple review articles and position statements support walking as beneficial and as the primary mode of exercise for patients with PAD (Gerhard-Herman *et al*, 2017; Hamburg and Balady, 2011; Askew *et al*, 2014). In a 1995 meta-analysis looking at exercise in patients with PAD, Gardner and Poehlman (1995) concluded that the optimal exercise program included intermittent walking at near maximal claudication pain. However, compliance is low and dropout rates are high with these types of exercise programs for patients with PAD (Bendermacher *et al*, 2007).

Patients with PAD who participate in supervised treadmill exercise programs show greater increases in maximal treadmill walking distance versus patients who participate in unsupervised home-based walking programs or who receive walking advice (Hageman *et al*, 2018). McDermott *et al* (2009) have demonstrated that patients with PAD show large improvements in maximal treadmill walking time (51%) when participating in supervised treadmill exercise interventions, yet only show minimal improvement (6.4%) in 6MWT distances. Conversely, patients with PAD who completed a home-based over ground walking program have shown an improvement (12%) in six-minute walk test distances nearly double that shown in the treadmill training program

(McDermott *et al*, 2013). This suggests there may be a specificity of the training mode such that patients who train on a treadmill show greater increases in treadmill performance measures and patients who train overground show greater improvement in the 6MWT distance.

The literature on supervised walking therapy for patients with PAD includes almost exclusively treadmill training. Conversely, the research on overground walking training includes almost exclusively unsupervised, home-based training. Six randomized controlled trials have reported the results of overground ambulation training in a supervised setting and all used treadmill testing for the primary walking outcomes (Fakhry *et al*, 2012). Four of these studies used other modes of exercise training in addition to overground walking, including upper and lower body exercises, and including both active and passive leg exercises (Dahllof *et al*, 1974; Tisi *et al*, 1997; Hobbs *et al*, 2006; Hobbs *et al*, 2007). One study used polestriding as the mode of exercise (Langbein *et al*, 2002). Including other modes of exercise or assistive devices with walking (e.g., polestriding) makes it difficult to truly measure the impact of supervised walking therapy. Lastly, only one trial used overground walking exclusively in a supervised setting (Gelin *et al*, 2001). This study compared a surgical intervention to supervised exercise and a control group. Only the surgical intervention group showed improvement in treadmill workload and distance, leg blood flow, and leg blood pressure. The supervised exercise and control groups did not improve in any of the outcome measures. The authors concluded that supervised exercise training offered no benefit compared to controls (Gelin *et al*, 2001). This study appears to highlight the importance of the specificity of training and using the appropriate outcome measure for functional capacity.

In addition, the unpublished study in chapter IV compared a novel combination treadmill and ambulation training protocol (COMBO) with a commonly used standard treadmill only training protocol (STAND) in patients with PAD. This was the first study to compare the difference between two training protocols on 6MWT performance in patients with PAD. The 6MWT total distance did not differ between the COMBO and STAND training protocols. However, both the 6MWT claudication onset distance and claudication onset time were greater in the COMBO group versus the STAND group. The results of this study suggest that ambulation training may improve 6MWT performance compared treadmill only training in patients with PAD.

Treadmill only training protocols are beneficial but may not be the optimal training protocol for patients with PAD and intermittent claudication. The treadmill protocol in the PAD Exercise Training Toolkit (AACVPR/VDF, 2010) includes a short warm-up period of 4-5 minutes and then introduces a training workload that is at or near the ischemic (claudication) threshold. The limited warm-up period and sudden intensity in workload has the potential to compromise performance, increase symptoms, and decrease both compliance to and enjoyment of the exercise. In addition, this protocol focuses on increasing treadmill incline (up to 10% or more) over increasing walking speed. The rationale is that patients with PAD generally walk at slow speeds due to their claudication symptoms and would tolerate a change in incline over a change in speed. Using treadmill only walking and including elevation changes not seen in normal daily life may not translate as well to ground walking or to everyday functional capacity as overground ambulation training.

An ideal exercise training protocol for a patient with PAD would include supervision, an extended warm-up period, progressive increases in workload and overground walking at speeds that mimic normal walking gait and translate to improved 6MWT performance. Including ambulation training in a supervised setting for patients with PAD may have the potential to improve six-minute walk test distance and meaningful clinical outcomes to a greater extent than treadmill training alone.

PASSIVE HEAT AND PERIPHERAL ARTERIAL DISEASE

The benefits of including walking exercise as the primary mode of treatment for patients with PAD are well established (Gerhard-Herman *et al*, 2017; Hamburg and Balady, 2011; Askew *et al*, 2014). Generally, any walking will improve patient outcomes, but supervised exercise therapy is superior to unsupervised exercise therapy (Fokkenrood *et al*, 2013). However, compliance is low and dropout rates are high with these types of exercise programs because patients are either unwilling or unable to tolerate the exercise due to the symptoms of claudication pain (Bendermacher *et al*, 2007). Finding alternative treatments for patients with PAD is critical to improve patient outcomes such as reduced cardiovascular events and mortality. Passive heat therapy has shown promise in improving cardiovascular health and function and may prove to be an important strategy in the treatment of patients with PAD.

Recent attention has been focused on the use of passive heat therapy to improve cardiovascular health and function. The impetus for this attention can be attributed to the results of a 30-year prospective study out of Finland showing that a lifetime of sauna use could reduce the risk of both cardiovascular-related and all-cause mortality (Laukkanen *et al*, 2015). There are a few published trials that have investigated passive heat interventions on patients with peripheral arterial disease. In 2007, Tei and colleagues published a research correspondence to the editor of the *Journal of the American College of Cardiology* purporting that the Waon therapy (a type of sauna therapy), which they developed years earlier for patients with heart failure, was now showing benefits for patients with PAD (Tei *et al*, 2007). In this study they used Waon therapy 5 days per week for 10 weeks on 20 patients with PAD and an ankle-brachial pressure index (ABI) of <0.9. The results showed that resting leg pain decreased, walking distance increased, and 7 pre-existing ulcers healed or significantly improved. Also, the ABI increased in almost every subject, which is remarkable since this is typically not expected with exercise training (Parmenter *et al*, 2010; Harwood *et al*, 2016). A few years later, this same research group showed that 6 weeks of Waon therapy increased the mobilization of CD34+ cells in patients with PAD (Shinsato *et al*, 2010). Increased CD34+ cells, characterized as endothelial progenitor cells, have been associated with improved vascular function and health. In one study, patients with PAD and critical limb ischemia avoided recommended amputation after injection of CD34+ cells (Subrammaniyan *et al*, 2011).

Recent studies have shown that acute bouts of passive heating can improve exercise performance in patients with PAD. Pellinger *et al* (2019) studied six patients with PAD under three randomized treatments conditions 2-7 days apart: bilateral lower leg heating for either 15 or 45 minutes, or control. Six-minute walk test distance increased 10% and 12% after 15- and 45-minute bouts of heating, respectively, compared to the control condition. Both improvements were clinically significant. In addition, popliteal artery blood flow increased under both heating conditions (Pellinger *et al*, 2019). More recently, Monroe *et al* (2021) randomized 16 patients with PAD in a crossover design to 90 minutes of lower-extremity heating or a sham treatment prior to a cardiopulmonary exercise test on a treadmill. Peak treadmill walking time improved in the heat therapy condition, but claudication onset time did not improve (Monroe *et al*, 2021).

The literature on the effects of chronic passive heat therapy on patients with PAD is small but gaining interest among researchers. Shinsato and colleagues (2010), in the same study that demonstrated improvements in ABI and CD34+ cells with Waon therapy, also showed a remarkable improvement in 6MWT distance of 81 m with only six weeks of Waon therapy in patients with PAD. Akerman *et al* (2019) compared 12-weeks of heat therapy versus supervised exercise in patients with PAD. The heat therapy group used whole-body water immersion at 39 degrees C, 3-5 days/week for ≤30 minutes, followed by ≤30 minutes of calisthenics. The exercise group walked or engaged in other modes of exercise for ≤90 minutes 1-2 days/week. Both groups showed a 41 m improvement in 6MWT distance, improvement in 6MWT pain-free walking distance, as well as decreases in resting blood pressure. There was no significant difference between groups in any of those three outcome measures (Akerman *et al*, 2019). Monroe *et al* (2020) studied the effect of 6 weeks of bilateral leg heat therapy with water-perfused trousers at 48 degrees C versus a sham treatment on 6MWT distance in patients with PAD. There was no difference between groups in the 6MWT distance; however, the heat therapy group reported a perceived improvement in physical function by scoring significantly higher than the sham group on the ’physical function’ subscale of the 36-item Short Form Health Survey (Monroe *et al*, 2020). Monroe and colleagues (2022) have more recently published a study looking at the effects of home-based lower-extremity heat therapy on walking performance in patients with PAD. Patients with claudication were randomized into leg heat therapy or sham. Patients in both groups were given water-perfusion trousers and a portable pump and were instructed to use the treatment for 90 minutes daily for 8 weeks. At the 8-week follow-up, the heat therapy group increased an average of 21 m in the 6MWT distance while the sham group showed no improvement. The benefits of passive heating on walking performance in patients with PAD will become clearer as the literature grows in this area.

DIRECTIONS FOR FUTURE RESEARCH

Peripheral arterial disease leads to an accelerated decline in physical function and patients with PAD have a high risk of morbidity and mortality. Improving functional capacity in patients with PAD is important to lower the risk of cardiovascular events and death. In addition to the recommended guidelines for exercise training for patients with PAD, future research studies should explore other interventions to augment the benefits of treadmill training in this population.

There appears to be a benefit to including ambulation training as part of the exercise protocol for patients with PAD. Supervised ambulation training has shown to improve 6MWT claudication onset distance and claudication onset time in patients with PAD. Further research is needed to test components of the exercise prescription, such as the duration and intensity, to identify optimal protocols for ambulation training and maximize functional capacity in patients with PAD.

Using passive heat may be another promising strategy to improve cardiovascular and health outcomes in patients with PAD. Acute bouts of passive heating and chronic passive heat therapy have both been shown to improve 6MWT distance in this patient population. Future studies should investigate the effect of passive heat as both a standalone treatment and as an adjunct treatment to exercise training in patients with PAD. In addition to functional capacity measurements, these studies should also include assessments of vascular function, lab work, and other physiological measurements to identify the underlying mechanisms leading to the improved performance.

Further research on ambulation training and on passive heat therapy can inform future treatments for patients with PAD. These and other novel approaches may challenge the current paradigm of primarily prescribing treadmill exercise training for patients with PAD by introducing and validating new techniques that could become part of standard practice and further improve outcomes in patients with PAD.

CHAPTER VII

CONCLUSIONS AND FUTURE DIRECTIONS

MAIN FINDINGS

Peripheral arterial disease represents an advanced burden of cardiovascular disease and patients with PAD have a high risk of morbidity and mortality. In addition, PAD leads to an accelerated decline in physical function and increased disability in both symptomatic and asymptomatic patients. The first line of treatment for patients with PAD, and without critical limb ischemia, is exercise and risk factor modification. Evidenced-based exercise guidelines recommend weight-bearing exercise, specifically walking in a supervised setting, as the primary mode of exercise. The primary purpose of this dissertation was to expand on the standard practice and explore novel exercise and other training techniques that could improve the outcomes of patients with PAD.

The study in chapter IV compared a novel combination treadmill and ambulation training protocol (COMBO) with a commonly used standard treadmill only training protocol (STAND) on patients with PAD. This was the first study to compare the difference between two training protocols on 6MWT performance in patients with PAD. The improvement in 6MWT total distance did not differ between the COMBO and STAND training protocols. However, both the 6MWT claudication onset distance and claudication onset time were greater in the COMBO group versus the STAND group. The results of this study suggest that ambulation training may improve 6MWT performance compared treadmill only training in patients with PAD.

The study in chapter V investigated the effect of an active walking warm-up on the results of the 6MWT distance in patients with PAD. The study was the first to assess the effect of an active warm-up on the 6MWT in patients with PAD. The 6MWT total distance did not differ between the WARM-UP and NO WARM-UP conditions. Additionally, neither the 6MWT claudication onset distance nor claudication onset time differed between the WARM-UP and NO WARM-UP conditions. The results of this study suggest that an active warm-up of 10-12 minutes of walking on a treadmill at a workload between 1.4-2.1 METs may not be enough of a stimulus to increase 6MWT distance in patients with PAD.

Chapter VI was a review article intended to explore novel exercise and other interventions that could challenge the current paradigm of exercise training for patients with PAD. This was accomplished by reviewing the literature showing improved outcomes, particularly 6MWT distance, with exercise in patients with PAD, discussing the current state of practice of PAD rehabilitation (SET for PAD), introducing overground ambulation in the supervised clinical setting, reviewing the literature on the effect of acute and chronic passive heating in patients with PAD, and discussing directions for future research with ambulation training and passive heating.

FUTURE DIRECTIONS

Walking exercise is well established as the primary mode of treatment for patients with PAD. However, many patients do not benefit from this treatment because they are either unwilling or unable to tolerate the exercise due to the symptoms of claudication pain. Finding alternative treatments for patients with PAD is critical to improve patient outcomes such as reduced cardiovascular events and mortality. Supervised ambulation training has shown to improve 6MWT performance to a greater extent than treadmill training. This improvement could be the difference between a modest patient outcome and a clinically meaningful outcome. In addition, passive heat therapy has shown promise in improving cardiovascular health and function and may prove to be an important strategy in the treatment of patients with PAD. Future research should introduce and explore novel training techniques that could further improve patient outcomes and become standard practice.

APPENDIX

INFORMED CONSENT DOCUMENTS

Chapter IV: Training Study and Chapter V: Acute Study

PeaceHealth

CONSENT TO PARTICIPATE IN RESEARCH

A Novel Peripheral Arterial Disease Combination Treadmill and Ambulation Training Protocol

Principal Investigator: Aaron Harding, MS, Clinical Exercise Physiologist
PeaceHealth Cardiac Rehabilitation
541-222-7216 phone
aharding@peacehealth.org

You are invited to participate in this study because you have been diagnosed with peripheral arterial disease (PAD) with intermittent claudication. Your participation in this research study is voluntary.

Why is this study being done?

The purpose of this study is to compare the risks and benefits of a new PAD treadmill training procedure with a commonly used treadmill training procedure. If the new procedure proves to be effective, it could provide clinicians an alternative, and possibly an improved, way to treat patients with PAD. In addition, this study will measure the effect of a warm-up on the outcome of the six-minute walk test.

What will happen if I take part in this research study?

If you decide to participate in this study, the researcher will ask you to do the following:

- Perform a six-minute walk test; receive blood pressure measurements on your arms and ankles; and complete a quality of life questionnaire prior to participating in a PAD rehabilitation program.
- Perform a second six-minute walk test on your second visit. A walking warm-up will be performed prior to either the first or the second six-minute walk test.
- Complete 20-36 exercise sessions within 12 weeks of a PAD rehabilitation program at the Oregon Heart & Vascular Institute at PeaceHealth in Springfield, Oregon. You will be randomly assigned to exercise for up to 60 minutes using either the new PAD treadmill and ambulation training protocol or the currently recommended PAD treadmill training protocol.
- Perform a final six-minute walk test; receive blood pressure measurements on your arms and ankles; and complete a quality of life questionnaire and an exercise enjoyment questionnaire after participating in a PAD rehabilitation program.

PeaceHealth System
Institutional Review Board
Approved 1/26/2022

How long will I be in the research study?

Participation will take a total of about 14-16 weeks. The initial assessments will be completed within 1-2 weeks prior to participating in the PAD rehabilitation program; and the follow-up assessments will be completed within 1-2 weeks after the PAD rehabilitation program ends. The PAD rehabilitation program will include 20-36 one-hour exercise sessions and last up to 12 weeks in duration, that's 2 or 3 one-hour exercise sessions a week.

You may be eligible for only part of the study and would perform a six-minute walk test on your first two visits. A walking warm-up would be performed prior to either the first or the second six-minute walk test. After the second visit, your involvement in the study would end and you could continue your enrollment in the PAD rehabilitation program.

Are there any potential risks or discomforts that I can expect from this study?

- The most likely risk or discomfort expected with study participation is the leg pain with walking associated with PAD, known as claudication.
- Other potential risks include fatigue, muscle soreness, or minor orthopedic injury.
- Rare cardiac events can occur with exercise including cardiac arrhythmias, heart attack or death.
- All exercise testing and exercise training will be overseen by trained clinical staff at PeaceHealth to minimize risks and to respond to emergencies.
- Other inconveniences may include your time invested and the potential financial cost to cover insurance co-pays or co-insurances to participate in the PAD rehabilitation program. The financial cost of participating in the study will not cost any more than participating in the PAD rehabilitation program only.
- You do not waive any liability rights for personal injury by signing this form. All forms of medical diagnosis and treatment, whether routine or experimental, involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the researchers will assist you in obtaining appropriate medical treatment, but PeaceHealth does not provide financial assistance for medical or other costs.
- You or your health insurance company will be billed for the costs of all care which are routine for your medical condition, unless otherwise specified in this consent. You will be responsible for co-payments and deductibles. If you are a Medicare beneficiary and you join a covered clinical research study, Medicare will pay for some routine costs, like office visits and tests. If you have opted for a Medicare Advantage plan, you get the same coverage as a person in Original Medicare. However, you should notify your plan to find out how the costs of care from being in this study are covered. For more information about Medicare coverage visit: https://www.medicare.gov/Pubs/pdf/02226-Medicare-and-Clinical-Research-Studies.pdf, or https://www.medicare.gov/coverage/clinical-research-studies.html or call 1-800-Medicare. For other health insurance company coverage, contact your plan.

Are there any potential benefits if I participate?

Many studies have shown that patients with PAD benefit from participating in supervised exercise programs. As a result of participation, you may potentially increase walking distance and walking time, improve quality of life and decrease risk of cardiovascular events.

You could potentially help others. The results of this research may provide clinicians with alternative, or possibly improved, exercise treatment protocols for patients with PAD

What other choices do I have if I choose not to participate?

If you decide not to participate in this research study, you may still enroll in and benefit from PAD rehabilitation. You may also decide not to participate in the study or in PAD rehabilitation.

Will information about me and my participation be kept confidential?

Any information that is obtained in connection with this study and that can identify you will remain confidential. It will be disclosed only with your permission or as required by law. Confidentiality will be maintained by means of assigning you a unique subject number upon entering the study.

Your subject number will be known only to the researchers. The code list, which connects your name to your subject number, will be locked in a file cabinet in the Oregon Heart & Vascular Institute at PeaceHealth. The principle investigator will be blind to the subject number code list. That means, when he analyzes the results of the study, he will only see the subject numbers. He won't see your name.

The code list will be destroyed after the results of the study are published or 24 months after the end of the study, whichever is first.

What are my rights if I take part in this study?

- You can choose whether you want to be in this study, and you may withdraw your consent and discontinue participation at any time.
- Whatever decision you make, there will be no penalty to you, and no loss of benefits to which you were otherwise entitled.
- You may refuse to answer any questions that you do not want to answer and still remain in the study.

Who can I contact if I have questions about this study?

- **The research team:**
  If you have any questions, comments or concerns about the research, you can talk to the one of the researchers. Please contact:

Aaron Harding, MS
Clinical Exercise Physiologist
Cardiac Rehabilitation
Oregon Heart & Vascular Institute
3311 RiverBend Drive
Springfield, OR 97477
541-222-7216 phone
aharding@peacehealth.org

- **PeaceHealth System Institutional Review Board:**
  If you have questions about your rights while taking part in this study, or you have concerns or suggestions and you want to talk to someone other than the researchers about the study, please call the IRB at (458) 205-6829 or email to: IRB@peacehealth.org.

You will be given a copy of this information to keep for your records.

SIGNATURE OF STUDY PARTICIPANT

____
Name of Participant

______________________________ __________________
Signature of Participant Date

SIGNATURE OF PERSON OBTAINING CONSENT

______________________________ __________________
Name of Person Obtaining Consent Contact Number

______________________________ __________________
Signature of Person Obtaining Consent Date

AUTHORIZATION TO USE AND DISCLOSE HEALTH INFORMATION

Chapter IV: Training Study and Chapter V: Acute Study

PeaceHealth System
Institutional Review Board
Approved 2/10/2021

PeaceHealth *Authorization to Use and Disclose Health Information*

Patient

Patient Name: ____________________

Birth Date: __________ Ph. #: __________ SSN: __________

From / To

I authorize the use and/or disclosure of the health information described below for the above-named patient by the following entities:

Information is to be released FROM:	Information is to be disclosed TO:
Cardiac Rehabilitation	Aaron Harding and John Halliwill, Co-Investigators
3311 RiverBend Drive	Michelle Sparks and Robert Stalbow, Key Study Personnel
Springfield, OR 97477	

Please specify the hospital, clinic, or practice holding the records.
PeaceHealth RiverBend -CareConnect EMR and Cardiac Rehabilitation Department

Purpose

For the purpose(s) of:
- ❑ At the request of the patient or legal/personal representative
- ■ Other purposes (specify each purpose): Research Study

Info to be Disclosed

Description of nature of information to be used and/or disclosed: (initial all that apply)

		Specially Protected Information:
____ Discharge summaries	____ Pathology reports	____ Mental health treatment records
____ History & Physical exams	____ Radiology/imaging reports	____ Drug/Alcohol abuse diagnosis, treatment, and referral records
____ Consultations	____ Laboratory reports	____ Information re: HIV/AIDS/Sexually transmitted diseases
____ Operative reports	____ EKG reports	____ Information re: Genetic testing (Oregon)
____ Physician progress notes	____ Emergency Dept. record	
____ Nursing notes	____ Medication records	
____ Clinician office notes	____ Billing statements	

____ Other information (specify): __________ ____ Records for the following dates or treatment: __________

x All health records from the above-named entity (Excludes above Specially Protected information unless indicated by initials)

Notices

1. I understand that, if the recipient of the information disclosed under this authorization is not a health plan or provider covered by federal or state privacy laws, the information may be re-disclosed by the recipient and no longer protected by those laws. If the information being disclosed under this authorization includes HIV/AIDS, Sexually Transmitted Diseases, mental health, genetic testing, and drug/alcohol abuse diagnosis, treatment, or referral information, Federal law and regulation including 42 CFR Part 2 and 445 CFR Parts 160 and 164 or state law may prevent the recipient from re-disclosing this information.
2. I may refuse to sign this authorization. My refusal will not adversely affect my ability to receive treatment, to enroll in a health plan, to be eligible for benefits, or to obtain payment for services unless this authorization is sought for purposes of research-related treatment, to determine my eligibility or enrollment in a plan, for underwriting or risk determinations or if the services related to the information to be disclosed are performed solely for the purpose of providing that information to someone else.
3. I may revoke this authorization at any time by notifying the Health Information Management/Medical Records Department of the above-named entity on its designated form. However, any such revocation will not apply to any activity undertaken based on this authorization. PeaceHealth's Joint Notice of Privacy Practices also describes how to revoke this authorization.
4. I received a copy of this authorization. I may inspect or request copies of information disclosed by this authorization.

Dates

Unless revoked, this authorization is valid for 90 days from the signature date below or for the following time period.
Beginning date: 1/1/2021 Ending (expiration) date: No end date
(In Washington state, expiration date can be no later than 1 year after this authorization is signed if disclosure is to employer or financial institution.)

Signature

SIGNATURE: I have read this authorization, and I understand it.

Signature of Patient or personal representative ____ Relationship to patient ____ Date ____

*If the patient's personal representative, you may be required to provide appropriate documentation to demonstrate authority to act on behalf of the patient (Examples of documentation include Power of Attorney, Death Certificate, Court order)

For PeaceHealth Use Only
Date Received: ______ MRUN # ______ Acct # ______ ❑ Identity and authority verified
❑ Fees explained if needed ❑ Records sent by ______ Date/Time: ______

Please don't write in box: Release of Information Authorization SYS1020 (03/29/18)

36-ITEM SHORT FORM QUESTIONNAIRE (SF-36)

Chapter IV: Training Study

Name____________________________________**Date**______________________________

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
▼	▼	▼	▼	▼
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very Severe
▼	▼	▼	▼	▼	▼
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

THANK YOU FOR COMPLETING THESE QUESTIONS!

PHYSICAL ACTIVITY ENJOYMENT SCALE (PACES)

Chapter IV: Training Study

Name:____ Date:______________

Physical Activity Enjoyment Scale

Please rate how you feel *at the moment* about the physical activity you have been doing.

1	2	3	4	5	6	7
I enjoy it						I hate it

1	2	3	4	5	6	7
I feel bored						I feel interested

1	2	3	4	5	6	7
I dislike it						I like it

1	2	3	4	5	6	7
I find it pleasurable						I find it unpleasurable

1	2	3	4	5	6	7
I am very absorbed in this activity						I am not at all absorbed in this activity

1	2	3	4	5	6	7
It's no fun all at						It's a lot of fun

1	2	3	4	5	6	7
I find it energizing						I find it tiring

1	2	3	4	5	6	7
It makes me depressed						It makes me happy

1	2	3	4	5	6	7
It's very pleasant						It's very unpleasant

1	2	3	4	5	6	7
I feel good physically while doing it						I feel bad physically while doing it

Kendzierski and DeCarlo, 1991. Journal of Sport & Exercise Psychology 13(1): 50-64.

Name:____ Date:_______________

1	2	3	4	5	6	7
It's very invigorating						It's not at all invigorating

1	2	3	4	5	6	7
I am very frustrated by it						I am not at all frustrated by it

1	2	3	4	5	6	7
It's very gratifying						It's not at all gratifying

1	2	3	4	5	6	7
It's very exhilarating						It's not at all exhilarating

1	2	3	4	5	6	7
It's not at all stimulating						It's very stimulating

1	2	3	4	5	6	7
It gives me a strong sense of accomplishment						It does not give me any sense of accomplishment

1	2	3	4	5	6	7
It's very refreshing						It's not at all refreshing

1	2	3	4	5	6	7
I felt as though I would rather be doing something else						I felt as though there was nothing else I would rather be doing

Kendzierski and DeCarlo, 1991. Journal of Sport & Exercise Psychology 13(1): 50-64.

REFERENCES CITED

Agnelli G, Belch JJF, Baumgertner I, Giovas P, Hoffmann U. Morbidity and mortality associated with atherosclerotic peripheral artery disease: a systematic review. *Atherosclerosis*. 2020; 293:94-100.

Akerman AP, Thomas KN, van Rij AM, Body ED, Alfadhel M, Cotter JD. Heat therapy vs. supervised exercise therapy for peripheral arterial disease: a 12-wk randomized, controlled trial. *Am J Physiol Heart Circ Physiol*. 2019; 316(6):H1495-H1506.

American Association of Cardiovascular and Pulmonary Rehabilitation/Vascular Disease Foundation. *PAD Toolkit – PAD Coalition; 2010*. Available from: www.vdf.org or www.aacvpr.org.

American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription*. 11th ed. Philadelphia (PA): Wolters Kluwer; 2022.

Anderson TJ, Uchata A, Gerhard MD, Meredith IT, Knab S, Delagrange D, Lieberman EH, Ganz P, Creager MA, Yeung AC, Selwyn AP. Close relation of endothelial function in the human coronary and peripheral circulations. *Am J Coll Cardiol*. 1995; 26: 1235-1241.

Andzel WD. The effects of moderate prior exercise and varied rest intervals upon cardiorespiratory endurance performance. *J Sports Med Phys Fitness*. 1978; 18:245-252.

Andzel WD. One mile run performance as a function of prior exercise. *J Sports Med Phys Fitness*. 1982; 22:80-84.

Askew CD, Parmenter B, Leicht AS, Walker PJ, Golledge J. Exercise & Sports Science Australia (ESSA) position statement on exercise prescription for patients with peripheral arterial disease and intermittent claudication. *J Sci Med Sport*. 2014; 17(6):623-629.

Asmussen E, Boje O. Body temperature and capacity for work. *Acta Physiol Scand*. 1945; 10:1-22.

ATS Statement: Guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002; 166:111-117.

Beattie DK, Golledge J, Greenhalgh RM, Davis AH. Quality of life assessment in vascular disease: towards a consensus. *Eur J Vasc Endovasc Surg*. 1997; 13(1):9-13.

Bendermacher BLW, Willigendeal EM, Teijink JAW, Prins MH. Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. *Cochrane Database Syst Rev*. 2006; CD005263.

Bendermacher BL, Willigendael EM, Nicolai SP, Kruidenier LM, Welten RJ, Hendriks E, Prins MH, Teijink JAW, de Bie RA. Supervised exercise therapy for intermittent claudication in a community-based setting is as effective as clinic-based. *J Vasc Surg*. 2007; 45:1192-1196.

Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P. Heart disease and stroke statistics – 2017 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2017; 135:e146-603.

Bennett AF. Thermal dependance of muscle function. *Am J Physiol*. 1984; 247:R217-R229.

Bergh U, Ekblom B. Influence of muscle temperature on maximal muscle strength and power output in human skeletal muscles. *Acta Physiol Scand*. 1979; 107:33-37.

Bergstrom J, Hermansen L, Hultman E, Saltin B. Diet, muscle glycogen and physical performance. *Acta Physiol Scand*. 1967; 71:140-150.

Binkhorst RA, Hoofd L, Vissers ACA. Temperature and force-velocity relationship of human muscles. *J Appl Physiol*. 1977; 42(4):471-475.

Bishop D, Bonetti D, Dawson B. The influence of three different warm up intensities on sprint kayak performance in trained athletes. *Med Sci Sports Exerc*. 2001; 33(6):1026-1032.

Bishop D. Warm up I: potential mechanisms and the effects of passive warm up on exercise performance. *Sports Med*. 2003a; 33(6):439-454.

Bishop D. Warm up II: performance changes following active warm up and how to structure the warm up. *Sports Med*. 2003b; 33(6):483-498.

Bronas UG, Treat-Jacobson D, Leon AS. Comparison of the effect of upper body-ergometry aerobic training vs treadmill training on central cardiorespiratory improvement and walking distance in patients with claudication. *J Vasc Surg*. 2011; 53:1557-1564.

Brunt VE, Howard MJ, Francisco MA, Ely BR, Minson CT. Passive heat therapy improves endothelial function, arterial stiffness and blood pressure in sedentary humans. *J Physiol*. 2016a; 594(18): 5329-5342.

Brunt VE, Eymann TM, Francisco MA, Howard MJ, Minson CT. Passive heat therapy improves cutaneous microvascular function in sedentary humans via improved nitric oxide-dependent dilation. *J Appl Physiol.* 2016b; 121: 716-723.

Bruyn-Prevost P, Lefebvre F. The effects of various warming up intensities and durations during a short maximal anaerobic exercise. *Eur J Appl Physiol*. 1980; 43:101-107.

Carlile F. Effect of preliminary passive warming up swimming performance. *Res Q Exerc Sport*. 1956; 27(2):143-151.

Carter HH, Spence AL, Atkinson CL, Pugh CJA, Naylor LH, Green DJ. Repeated core temperature elevation induces conduit artery adaptation in humans. *Eur J Appl Physiol.* 2014; 114: 859-865.

Celermajer DS, Sorenson KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID, Lloyd JK, Deanfield JE. Noninvasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet.* 1992; 340: 1111-1115.

Cheetham DR, Burgess L, Ellis M, Williams A, Greenhalgh RM, Davies AH. Does supervised exercise offer adjuvant benefit over exercise advice alone for the treatment of intermittent claudication? *Eur J Vasc Endovasc Surg*. 2004; 27:17-23.

Clarke RSJ, Hellon RF, Lind AR. The duration of sustained contractions of the human forearm at different muscle temperatures. *J Physiol*. 1958; 143:454-473.

CMS Decision Memo. Decision memo for Supervised Exercise Therapy (SET) for Symptomatic Peripheral Artery Disease (PAD) (CAG-00449N). May 25, 2017. https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=287.

Collins TC, Lunos S, Carlson T, Henderson K, Lightbourne M, Nelson B, Hodges JS. Effects of a home-based walking intervention on mobility and quality of life in people with diabetes and peripheral arterial disease: a randomized controlled trial. *Diabetes Care*. 2011; 34(10):2174-2179.

Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, Browner D. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med*. 1992; 326:381-386.

Dahllof AG, Bjorntorp P, Holm J, Schersten T. Metabolic activity of skeletal muscle in patients with peripheral arterial insufficiency: effect of physical training. *Eur J Clin Invest (Berl)*. 1974; 9-15.

Davies CTM, Young K. Effect of temperature on the contractile properties and muscle power of triceps surae in humans. *J Appl Physiol*. 1983; 55(1):191-195.

Dawson B, Goodman C, Lawrence S, Preen D, Polglaze T, Fitzsimons M, Fournier P. Muscle phosphocreatine repletion following single and repeated short sprint efforts. Scand J Med Sci Sports. 1997: 7:206-213.

de Liefde II, Hoeks SE, van Gestel YR, Klein J, Bax JJ, Verhagen HJM, Van Domburg RT, Poldermans D. The prognostic value of impaired walking distance on long-term outcome in patients with known or suspected peripheral arterial disease. *Eur J Vasc Endovasc Surg*. 2009; 38:482-487.

de Liefde II, Van Domburg RT, Bax JJ, Klein J, Verhagen HJM, Poldermans D. A decline in walking distance predicts long-term outcome in patients with known or suspected peripheral arterial disease. *Eur J Cardiovasc Prev Rehabil*. 2010; 17:321-328.

Degischer S, Labs KH, Hochstrasser J, Aschwanden M, Tschoepl M, Jaeger KA. Physical training for intermittent claudication: a comparison of structured rehabilitation versus home-based training. *Vasc Med*. 2002; 7:105-109.

Dolan P, Greig C, Sargeant AJ. Effect of active and passive warm-up on maximal short-term power output of human muscle [abstract]. *J Physiol*. 1985; 365:P74.

Edwards RHT, Harris RC, Hultman E, Kaijser L, Koh D, Nordesjo LO. Effect of temperature on muscle energy metabolism and endurance during successive isometric contractions, sustained to fatigue, of the quadriceps muscle in man. *J Physiol*. 1972; 220:335-352.

Ehrman JK, Lui K, Treat-Jacobson D. Supervised exercise training for symptomatic peripheral artery disease. *J Clin Exer Physiol*. 2017: 6(4):78-83.

Fakhry F, van de Luijtgaarden MD, Bax L, den Hoed PT, Hunink MGM, Rouwet EV, Spronk S. Supervised walking therapy in patients with intermittent claudication, *J Vasc Surg*. 2012; 56(4):1132-1142.

Ferguson RA, Ball D, Sargeant AJ. Effect of muscle temperature on rate of oxygen uptake during exercise in humans at different contraction frequencies. *J Exp Biol*. 2002; 205:981-987.

Feringa HHH, Bax, JJ, Hoeks S, van Waning VH, Elhendy A, Karagiannis S, Vidakovic R, Schouten O, Boersma E, Poldermans D. *Arch Intern Med*. 2007;167(22):2482-2489.

Fokkenrood HJP, Bendermacher BLW, Lauret GJ, Willigendeal EM, Prins MH, Teijink JAW. Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. *Cochrane Database Syst Rev*. 2013; 8:CD005263.

Fortney S, Wenger C, Bove J, Nadel ER. Effect of hyperosmolality on control of blood flow and sweating. *J Appl Physiol*. 1984; 57:1688-1695.

Franks BD. Physical warm-up. In: *Williams MH, editor. Ergogenic aids in sport*. Champaign (IL): Human Kinetic Publishers. 1983:340-375.

Ganio MS, Brothers RM, Shibata S, Hastings JL, Crandall CG. Effect of passive heat stress on arterial stiffness. *Exp Physiol.* 2011; 96: 919-926.

Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain. A meta-analysis. *JAMA*. 1995; 274:975-980.

Gardner AW, Katzel LI, Sorkin JD, Bradham DD, Hochberg MC, Flinn WR, Goldberg AP. Exercise rehabilitation improves functional outcomes and peripheral circulation in patients with intermittent claudication: a randomized controlled trial. *J Am Geriatr Soc*. 2001; 49:755-762.

Gardner AW, Montgomery PS, Scott KJ, Afaq A, Blevins SM. Patterns of ambulatory activity in subjects with and without intermittent claudication. *J Vasc Surg*. 2007; 46:1208-1214.

Gardner AW, Montgomery PS, Parker DE. Physical activity is a predictor of all-cause mortality in patients with intermittent claudication. J Vasc Surg. 2008; 47:117–22.

Gardner AW, Parker DE, Montgomery PS, Scott KJ, Blevins SM. Efficacy of quantified home-based exercise and supervised exercise in patients with intermittent claudication: a randomized controlled trial. *Circulation*. 2011; 123(5):491-498.

Gardner AW, Parker DE, Montgomery PS, Blevins SM. Step-monitored home exercise improves ambulation, vascular function, and inflammation in symptomatic patients with peripheral artery disease: a randomized controlled trial. *J Am Heart Assoc*. 2014; 3(5):e001107.

Gardner AW, Montgomery PS, Wang M. Minimal clinically important differences in treadmill, 6-minute walk, and patient-based outcomes following supervised and home-based exercise in peripheral artery disease. *Vasc Med*. 2018; 23(4):349-357.

Garg PK, Tian L, Criqui MH, Liu K, Ferrucci L, Guralnik JM, Tan J, McDermott MM Physical activity during daily life and mortality in patient with peripheral arterial disease. *Circulation*. 2006; 114:242-248.

Gelin J, Jivegard L, Taft C, Karlsson J, Sullivan M, Dahllof AG, Sandstrom R, Arfvidsson B, Lundholm K. Treatment efficacy of intermittent claudication by surgical intervention, supervised physical exercise training compared to no treatment in unselected randomized patients I: one year results of functional and physiological improvements. *Eur J Vasc Endovasc Surg*. 2001; 22:107-113.

Genovely H, Stamford BA. Effects of prolonged warm-up exercise above and below anaerobic threshold on maximal performance. *Eur J Appl Physiol*. 1982; 48:323-330.

Gerbino A, Ward S, Whipp B. Effects of prior exercise on pulmonary gas-exchange kinetics during high-intensity exercise in humans. J Appl Physiol. 1996; 80(1):99-107.

Gerhard-Herman MD, Gornik HL, Barrett C, Barshes, NR, Corriere MA, Drachman DE, Fleisher LA, Fowkes FGR, Hamburg NM, Kinlay S, Lookstein R, Misra S, Mureebe R, Olin JW, Patel RAG, Regensteiner JG, Schanzer A, Shishehbor MH, Stewart K, Treat-Jacobson T, Walsh ME. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2017; 69(11):1465-1508.

Gregson W, Batterham A, Drust, Cable NT. The effects of pre-warming on the metabolic and thermoregulatory responses to prolonged intermittent exercise in moderate ambient temperatures. *J Sports Sci*. 2002a; 20(1):49-50.

Gregson W, Drust B, Batterham A, Cable NT. The effects of pre-warming on the metabolic and thermoregulatory responses to prolonged submaximal exercise in moderate ambient temperatures. *Eur J Appl Physiol*. 2002b; 86:526-33.

Grodjinovsky A, Magel JR. Effect of warming-up on running performance. *Res Q Exerc Sport*. 1970; 41(1):116-119.

Gullich A, Schmidtbleicher D. MVC-induced short-term potentiation of explosive force. *New Stud Athletics*. 1996; 11(4):67-81.

Hageman D, Fokkenrood HJP, Gommans LNM, van der Houten MML, Teijink JAW. Supervised exercise therapy versus home-based exercise therapy versus walking advice for intermittent claudication. *Cochrane Database Syst Rev*. 2018; 4(4):CD005263.

Hamburg NM, Balady GJ. Exercise rehabilitation in peripheral artery disease: functional impact and mechanisms of benefits. *Circulation*. 2011; 123(1):87-97.

Hannuksela ML, Ellahham S. Benefits and risks of sauna bathing. *Am J Med.* 2001; 110(2): 118-126.

Harwood AE, Cayton T, Sarvanandan R, Lane R, Chetter I. A review of the potential local mechanisms by which exercise improves functional outcomes in intermittent claudication. *Ann Vasc Surg*. 2016; 30:312-320.

Hasan J, Karvonen MJ, Piironen P. Special Review. Part I: Physiological effects of extreme heat as studied in the Finnish "sauna" bath. *Am J Phys Med.* 1966; 45(6): 296-314.

Hawley JA, Williams MM, Hamling GC, Walsh RM. Effects of a task-specific warm-up on anaerobic power. *Br J Sports Med*. 1989; 23(4):233-236.

Hiatt WR, Wolfel EE, Meier RH, Regensteiner JG. Superiority of treadmill walking exercise versus strength training for patients with peripheral arterial disease: implications for the mechanism of the training response. *Circulation*. 1994; 90:1866-1874.

Hiatt WR, Rogers RK, Brass EP. The treadmill is a better functional test than the 6-minute walk test in therapeutic trails of patients with peripheral artery disease. *Circulation*. 2014; 130:69-78.

Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, Krook SH, Hunninghake DB, Comerota AJ, Walsh ME, McDermott MM, Hiatt WR. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA*. 2001; 286:1317-1324.

Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, Hiratzka LF, Murphy WR, Olin JW, Puschett JB, Rosenfield KA, Sacks D, Stanley JC, Taylor LM Jr, White CJ, White J, White RA, Antman EM, Smith SC Jr, Adams CD, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Hunt SA, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic). *Circulation,* 2006; 113:e463-e654.

Hirsch AT, Hartman L, Town RJ, Virnig BA. National health care costs of peripheral arterial disease in the Medicare population. *Vasc Med*. 2008; 13:209-215.

Hirvonen J, Rehunen S, Rusko H, Harkonen M. Breakdown of high-energy phosphate compounds and lactate accumulation during short supramaximal exercise. *Eur J Appl Physiol*. 1987; 56:253-259.

Hobbs SD, Marshall T, Fegan C, Adam DJ, Bradbury AW. The constitutive procoagulant and hypofibrinolytic state in patients with intermittent claudication due to infrainguinal disease significantly improves with percutaneous transluminal balloon angioplasty. *J Vasc Surg*. 2006; 43:40-46.

Hobbs SD, Marshall T, Fegan C, Adam DJ, Bradbury AW. The effect of supervised exercise and cilostazol on coagulation and fibrinolysis in intermittent claudication: a randomized controlled trial. *J Vasc Surg*. 2007; 45: 65-70.

Hotta K, Batchelor WB, Graven J, Dahva V, Noel TE, Ghai A, Katopodis JN, Dixon WC, Andrews R, Pragle A, Chheda J, Liberatore L, Behnke BJ, Muller-Delp, J. Daily passive muscle stretching Improves Flow-Mediated Dilation of Popliteal Artery and 6-minute walk test in elderly patients with stable symptomatic peripheral artery disease. *Cardiovasc Revasc Med*. 2019; 20(8):642-648.

IJzerman RG, de Jongh RT, Beijk MA, van Weissenbruch MM, Delemarre-van de Waal HA, Serne EH, Stehouwer CD. Individuals at increased coronary heart disease risk are characterized by an impaired microvascular function in skin. *Eur J Clin Invest.* 2003; 33: 536-542.

Imamura M, Biro S, Kihara T, Yoshifuku S, Takasaki K, Otsuji Y, Minagoe S, Toyama Y, Tei C. Repeated thermal therapy improves impaired vascular endothelial function in patients with coronary risk factors. *J Am Coll Cardiol*. 2001; 38(4): 1083-1088.

Inaba Y, Chen JA, Bergmann SR. Prediction of future cardiovascular outcomes by flow-mediated vasodilatation of brachial artery: a meta-analysis. *Int J Cardiovasc Imaging*. 2010; 26(6):631-640.

Joannides R, Haefeli WE, Linder L, Richard V, Bakkali EH, Thuillez C, Lüscher TF. Nitric oxide is responsible for flow-dependent dilatation of human peripheral conduit arteries in vivo. *Circulation.* 1995; 91: 1314-1319.

Karlsson J, Diamont B, Saltin B. Muscle metabolites during submaximal and maximal exercise in man. *Scand J Clin Lab Invest*. 1971; 26:385-394.

Kihara T, M, Biro S, Imamura M, Yoshifuku S, Takasaki K, Ikeda Y, Otsuji Y, Minagoe S, Toyama Y, Tei C. Repeated sauna treatment improves vascular endothelial function and cardiac function in patients with chronic heart failure. *J Am Coll Cardiol.* 2002; 39(5): 754-759.

Kozlowski S, Brzezinska Z, Kruk B, Kaciuba-Uscilko H, Greenleaf JE, Nazar K. Exercise hyperthermia as a factor limiting physical performance: temperature effect on muscle metabolism. *J Appl Physiol*. 1985; 59(3):766-773.

Kukkonen-Harjula K, Oja P, Laustiola K, Vuori I, Jolkkonen J, Siitonen S, Vapaatalo H. Haemodynamic and hormonal responses to heat exposure in a Finnish sauna bath. *Eur J Appl Physiol Occup Physiol.* 1989; 58(5): 543-550.

Kunutsor SK, Khan H, Laukkanen T, Laukkanen JA. Joint association of sauna bathing and cardiorespiratory fitness on cardiovascular and all-cause mortality risk: a long-term prospective cohort study. *Ann Med.* 2018; 50(2): 139-146.

Langbein WE, Collins EG, Orebaugh C, Maloney C, Williams KJ, Littooy FN, Edwards LC. Increasing exercise tolerance of persons limited by claudication pain using polestriding. *J Vasc Surg*. 2002; 35(5):887-893.

Laukkanen T, Khan H, Zaccardi F, Laukkanen JA. Association between sauna bathing and fatal cardiovascular and all-cause mortality events. *JAMA Intern Med.* 2015; 175: 542-548.

Laukkanen JA, Laukkanen T, Kunutsor SK. Cardiovascular and other health benefits of sauna bathing: A review of the evidence. *Mayo Clin Proc.* 2018; 93(8): 1111-1121.

Lee DT, Haymes EM. Exercise duration and thermoregulatory responses after whole body precooling. *J Appl Physiol*. 1995; 79(6):1971-1976.

Lee E, Laukkanen T, Kunutsor SK, Khan H, Willeit P, Zaccardi F, Laukkanen JA. Sauna exposure leads to improved arterial compliance: findings from a non-randomised experimental study. *Eur J Prev Cardiol*. 2018; 25(2);130-138.

Luurila OJ. The sauna and the heart. *J Intern Med.* 1992; 231(4): 319-320.

Margaria R, Prampero PE, Aghemo P, Derevenco P, Mariani M.

Massey BH, Johnson WR, Kramer GF. Effect of warm-up exercise upon muscular performance using hypnosis to control the psychological variable. *Res Q Exerc Sport*. 1961; 32:63-71.

McDermott MM, Greenland P, Liu K, Guralnik JM, Criqui MH, Dolan NC, Chan C, Celic L, Pearce WH, Schneider JR, Sharma L, Clark E, Gibson D, Martin GJ. Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. *JAMA*. 2001; 286:1599-1606.

McDermott MM, Ferrucci L, Simonsick EM, Balfour J, Fried L, Ling S, Gibson D, Guralnik JM. The ankle brachial index and change in lower extremity functioning over time: the Women's Health and Aging Study. *J Am Geriatr Soc*. 2002; 50:238-246.

McDermott MM, Guralnik JM, Ferrucci L, Tian L, Liu K, Liao Y, Green D, Sufit R, Hoff F, Nishida T, Sharma L, Pearce WH, Schneider JR, Criqui MH. Asymptomatic peripheral arterial disease is associated with more adverse lower extremity characteristics than intermittent claudication. *Circulation*. 2008a; 117:2483-2491.

McDermott MM, Tian L, Lui K, Guralnik JM, Ferrucci L, Tan J, Pearce WH, Schneider JR, Criqui MH. Prognostic value of functional performance for mortality in patients with peripheral artery disease. *J Am Coll Cardiol*. 2008b; 51:1482-1489.

McDermott MM, Ades P, Dyer A, Guralnik JM, Kibbe M, Criqui MH. Corridor-based functional performance measures correlate better with physical activity during daily life than treadmill measures in persons with peripheral arterial disease. *J Vasc Surg*. 2008c; 48:1231-1237.

McDermott MM, Ades P, Guralnik JM, Dyer A, Ferrucci L, Liu K, Nelson M, Lloyd-Jones D, Van Horn L, Garside D, Kibbe M, Domanchuk K, Stein JH, Liao Y, Tao H, Green D, Pearce WH, Scheider JR, McPherson D, Laing ST, McCarthy WJ, Shroff A, Criqui MH. Treadmill exercise and resistance training in patients with peripheral arterial disease with and without intermittent claudication: a randomized controlled trial. *JAMA*. 2009; 301(2):165-174.

McDermott MM, Liu K, Ferrucci L, Tian L, Guralnik JM, Criqui MH. Decline in functional performance predicts later increased in mobility loss and mortality in peripheral arterial disease. *J Am Coll Cardiol*. 2011; 57:962-970.

McDermott MM, Liu K, Guralnik JM, Criqui MH, Spring B, Tian L, Domanchuk K, Ferrucci L, Lloyd-Jones D, Kibbe M, Tao H, Zhao L, Liao Y, Rejeski WJ. Home-based walking exercise intervention in peripheral arterial disease: a randomized clinical trial. *JAMA*. 2013; 310:57-65.

McDermott MM, Guralnik JM, Criqui MH, Liu K, Kibbe MR, Ferrucci L. Six-minute walk is a better outcome measure than treadmill walking tests in therapeutic trials of patients with peripheral artery disease. *Circulation*. 2014; 130:61-68.

McDermott MM. Exercise Training for Intermittent Claudication. *J Vasc Surg*. 2017; 66(5):1612-1620.

McDermott MM, Spring B, Berger JS, Treat-Jacobson D, Conte MS, Creager MA, Criqui MH, Ferrucci L, Gornik HL, Guralnik JM, Hahn EA, Henke P, Kibbe MR, Kohlman-Trighoff D, Li L, Lloyd-Jones D, McCarthy W, Polonsky TS, Skelly C, Tian L, Zhao L, Zhang D, Rejeski WJ. Effect of a home-based exercise intervention of wearable technology and telephone coaching on walking performance in peripheral artery disease: the HONOR randomized clinical trial. *JAMA*. 2018; 319:1665-1676.

Mitchell GF, Hwang S-J, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, Vita JA, Levy D, Benjamin EJ. Arterial stiffness and cardiovascular events: The Framingham heart study. *Circulation.* 2010; 121: 505-511.

Monroe JC, Lin C, Perkins SM, Han Y, Wong BJ, Motaganahalli RL, Roseguini BT. Leg heat therapy improves perceived physical function but does not enhance walking capacity or vascular function in patients with peripheral artery disease. *J Appl Physiol (1985)*. 2020; 129(6):1279-1289.

Monroe JC, Song Q, Emery MS, Hirai DM, Motaganahalli RL, Roseguini BT. Acute effects of leg heat therapy on walking performance and cardiovascular and inflammatory responses to exercise in patients with peripheral artery disease. *Physiol Rep*. 2021; 8(24):e14650.

Monroe JC, Pae BJ, Kargl C, Gavin TP, Parker J, Perkins SM, Han Y, Klein J, Motaganahalli RL, Roseguini BT. Effects of home-based leg heat therapy on walking performance in patients with symptomatic peripheral artery disease: a pilot randomized trial. *J Appl Physiol (1985)*. 2022; 133(3): 546-560.

Montgomery PS, Gardner AW. The clinical utility of a six-minute walk test in peripheral arterial occlusive disease patients. *J Am Geriatr Soc*. 1998; 46(6):706-711.

Muido L. The influence of body temperature on performance in swimming. *Acta Physiol Scand*. 1946; 12:102-109.

Murabito JM, D'Agostino RB, Silbershatz H, Wilson WF. Intermittent claudication: A risk profile from The Framingham Heart Study. *Circulation*. 1997; 96(1):44-49.

Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER, Cohen DJ, Reynolds MR, Massaro JM, Lewis BA, Cerezo J, Oldenburg NC, Thum CC, Goldberg S, Jaff MR, Steffes MW, Comerota AJ, Ehrman J, Treat-Jacobson D, Walsh ME, Collins T, Badenhop DT, Bronas U, Hirsch AT. Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease: six-month outcomes from the claudication: exercise versus endoluminal revascularization (CLEVER) study. *Circulation*. 2012; 125:130-139.

Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER, Cohen DJ, Reynolds MR, Massaro JM, Lewis BA, Cerezo J, Oldenburg NC, Thum CC, Jaff MR, Comerota AJ, Steffes MW, Abrahamsen IH, Goldberg S, Hirsch AT. Supervised exercise, stent revascularization, or medical therapy for claudication due to aortoiliac peripheral artery disease: the CLEVER study. *J Am Coll Cardiol*. 2015; 314:1936-1944.

Nadel ER. Prolonged exercise and high and low ambient temperatures. *Can J Sport Sci*. 1987; 12(3 Suppl. 1):140S-142S.

Neff D, Kuhlenhoelter AM, Lin C, Wong BJ, Motaganahalli RL, Roseguini BT. Thermotherapy reduces blood pressure and circulating endothelin-1 concentration and enhances leg blood flow in patients with symptomatic peripheral arterial disease. *Am J Physiol Regul Integr Comp Physiol.* 2016; 311(2): R392-R400.

O'Brien B, Payne W, Gastin P, Burge C. A comparison of active and passive warm ups on energy system contribution and performance in moderate heat. *Aust J Sci Med Sport*. 1997; 29(4):106-109.

Ohori T, Nozawa T, Ihori H, Shida T, Sobajima M, Matsuki A, Yasumura S, Inoue H. Effect of repeated sauna treatment on exercise tolerance and endothelial function in patients with chronic heart failure. *Am J Cardiol.* 2012; 109(1): 100-104.

Olin JW. Can functional performance be used as a simple prognostic indicator in peripheral arterial disease? *Nat Clin Pract Cardiovasc Med*. 2008; 5:686-687.

Ozyener F, Rossiter HB, Ward SA, Whipp BJ. Influence of exercise intensity on the on- and off-transient kinetics of pulmonary oxygen uptake in humans. *J Physiol*. 2001; 533(3): 891-902.

Parmenter BJ, Raymond J, Fiatarone Singh MA. The effect of exercise on haemodynamics in intermittent claudication: a systematic review of randomized controlled trials. *Sports Med*. 2010; 40:433-447.

Parmenter BJ, Raymond J, Dinnen P, Singh MA. A systematic review of randomized controlled trials: walking versus alternative exercise prescription as treatment for intermittent claudication. *Atherosclerosis*. 2011; 218(1):1-12.

Parmenter BJ, Raymond J, Dinnen P, Lusby RJ, Fiatarone Singh MA. High-intensity progressive resistance training improves flat-ground walking in older adults with symptomatic peripheral arterial disease. *J Am Geriatr Soc*. 2013; 61:1964-1970.

Parmenter BJ, Dieberg G, Smart NA. Exercise training for management of peripheral arterial disease: a systematic review and meta-analysis. *Sports Med*. 2015; 45:231-244.

Pellinger TK, Neighbors MS, Simmons GH. Acute lower leg heating increases exercise capacity in patients with peripheral artery disease. *J Cardiovasc Nurs*. 2019; 24(2): 130-133.

Ratatunga KW, Sharpe B, Turnbull B. Contractions of human skeletal muscle at different temperatures. *J Physiol*. 1987; 390:383-395.

Regensteiner JG, Meyer TJ, Krupski WC, Cranford LS, Hiatt WR. Hospital vs home-based exercise rehabilitation for patients with peripheral arterial occlusive disease. *Angiology*. 1997; 48:291-300.

Ritti-Dias RM, Wolosker N, de Moraes Forjaz CL, Carvalho CR, Cucato GG, Leao PP, de Fatima Nunes Marucci M. Strength training increases walking tolerance in intermittent claudication patients: randomized trial. *J Vasc Surg*. 2010; 51:89-95.

Saltin B, Gagge AP, Stolwijk JAJ. Muscle temperature during submaximal exercise in man. *J Appl Physiol*. 1968; 25:679-688.

Sanderson B, Askew C, Stewart I, Walker P, Gibbs H, Green S. Short-term effects of cycle and treadmill training on exercise tolerance in peripheral arterial disease. *J Vasc Surg*. 2006; 44:119-127.

Sargeant AJ, Dolan P. Effect of prior exercise on maximal short-term power output in humans. *J Appl Physiol*. 1987; 63(4):1475-1480.

Savage P, Ricci MA, Lynn M, Gardner A, Knight S, Brochu M, Ades P. Effects of home versus supervised exercise for patients with intermittent claudication. *J Cardiopulm Rehabil*. 2001; 21:152-157.

Sax FL, Cannon RO III, Hanson C, Epstein SE. Impaired forearm vasodilator reserve in patients with microvascular angina. Evidence of a generalized disorder of vascular function? *N Engl J Med.* 1987; 317: 1366-1370.

Schiano V, Brevetti G, Sirico G, Silvestro A, Giugliano G, Chiariello M. Functional status measured by walking impairment questionnaire and cardiovascular risk prediction in peripheral arterial disease: results of the Peripheral Arteriopathy and Cardiovascular Events (PACE) study. *Vasc Med*. 2006; 11:147-154.

Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. *Circulation*. 2004; 110:738-743.

Shinsato T, Miyata M, Kubozono T, Ikeda Y, Fujita S, Kuwahata S, Akasaki Y, Hamasaki S, Fujiwara H, Tei C. Waon therapy mobilizes CD34+ cells and improves peripheral arterial disease. *J Cardiol.* 2010; 56(3): 361-366.

Stewart IB, Sleivert GG. The effect of warm-up intensity on range of motion and anaerobic performance. *J Orthop Sports Phys Ther*. 1998; 27(2):154-161.

Stewart KJ, Hiatt WR, Regensteiner JG, Hirsch AT. Exercise training for claudication. *N Engl J Med*. 2002; 347:1942-1951.

Subrammaniyan R, Amalorpavanathan J, Shankar R, Rajkumar M, Baskar S, Manjunath SR, Senthilkumar R, Murugan P, Srinivasan VR, Abraham S. Application of autologous bone marrow mononuclear cells in six patients with advanced critical limb ischemia as a result of diabetes: our experience. *Cytotherapy.* 2011; 13(8): 993-999.

Tei C, Shinsato T, Miyata M, Kihara T, Hamasaki S. Waon Therapy improves peripheral arterial disease. *J Am Coll Cardiol.* 2007; 50: 2169-2171.

Tew G, Nawaz S, Zwierska I, Saxton JM. Limb-specific and cross-transfer effects of arm-crank exercise training in patients with symptomatic peripheral arterial disease. *Clin Sci (Lond)*. 2009; 117:405-413.

Thijssen DHJ, Black MA, Pyke KE, Padilla J, Atkinson G, Harris RA, Parker B, Widlansky ME, Tschakovsky ME, Green DJ. Assessment of flow-mediated dilation in humans: a methodological and physiological guideline. *Am J Physiol Heart Circ Physiol*. 2011; 300: H2-H12.

Thomas KN, van Rij AM, Lucas SJE, Gray AR, Cotter JD. Substantive hemodynamic and thermal strain upon completing lower-limb hot-water immersion; comparisons with treadmill running. *Temperature.* 2016; 3(2): 286-297.

Thomas KN, van Rij AM, Lucas SJE, Cotter JD. Lower-limb hot-water immersion acutely induces beneficial hemodynamic and cardiovascular responses in peripheral arterial disease and healthy, elderly controls. *Am J Physiol Regul Integr Comp Physiol.* 2017; 312: R281-R291.

Tisi PV, Hulse M, Chulakadabba A, Gosling P, Shearman CP. Exercise training for intermittent claudication: does it adversely affect biochemical markers of the exercise-induced inflammatory response? *Eur J Vasc Endovasc Surg*. 1997; 14:344-350.

Treat-Jacobson D, Bronas UG, Leon AS. Efficacy of arm-ergometry versus treadmill exercise training to improve walking distance in patients with claudication. *Vasc Med*. 2009; 14:203-213.

Treat-Jacobson D, McDermott MM, Bronas UG, Campia U, Collins TC, Criqui MH, Gardner AW, Hiatt WR, Regensteiner JG, Rich K, on behalf of the American Heart Association Council on Peripheral Vascular Disease, Council on Quality of Care and Outcomes Research, and Council on Cardiovascular and Stroke Nursing. *Circulation*. 2019; 139(4):e10-e33.

Verma S, Buchanan MR, Anderson TJ. Endothelial function testing as a biomarker of vascular disease. *Circulation.* 2003; 108: 2054-2059.

Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol.* 2010; 55: 1318-1327.

Vuori, I. Sauna bather’s circulation. *Ann Clin Res.* 1988; 20(4):249-256.

Walker RD, Nawaz S, Wilkinson CH, Saxton JM, Pockley AG, Wood RF. Influence of upper- and lower-limb exercise training on cardiovascular function and walking distances in patients with intermittent claudication. *J Vasc Surg*. 2000; 31:662-669.

Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992: 30:473-483.

Watson L, Ellis B, Leng GC. Exercise for intermittent claudication. *Cochrane Database Syst Rev*. 2008 CD000990.

Young WB, Jenner A, Griffiths K. Acute enhancement of power performance from heavy load squats. *J Strength Cond Res*. 1998; 12:82-84.

Zwierska I, Walker RD, Choksy SA, Male JS, Pockley AG, Saxton JM. Upper- vs lower-limb aerobic exercise rehabilitation in patients with symptomatic peripheral arterial disease: a randomized controlled trial. *J Vasc Surg*. 2005; 42:1122-1130.