

EFFECTS OF PERIPHERAL REVASCULARIZATION ON BLOOD PRESSURE AND
CALF MUSCLE OXYGEN SATURATION IN PERIPHERAL ARTERY DISEASE

A Thesis
by
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Abstract

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Peripheral artery disease (PAD) reduces oxygen supply to exercising skeletal muscle in the lower extremity due to atherosclerotic reductions in blood flow. During exercise, a feedback mechanism sensitive to metabolic and mechanical stimuli, known as the exercise pressor reflex, serves to redistribute blood flow to active skeletal muscle. However, in individuals with PAD, there is an exaggerated exercise pressor reflex in response to lower extremity exercise thought to be caused, in part, by compromised blood flow. Endovascular and surgical revascularization procedures have been important for treating impaired limb perfusion caused by moderate to severe PAD. However, to what extent these procedures improve tissue perfusion during exercise or normalize the exercise pressor reflex remains unknown. Purpose: To examine whether revascularization reduces the exercise pressor reflex and improves skeletal muscle oxygen saturation (SmO_2) measured using near-infrared spectroscopy (NIRS) in the leg during foot exercise in patients with PAD. Methods:

Patients with symptomatic PAD (n = 6) performed incremental supine plantar flexion exercise, starting at 0.5 kg and increased by 0.5 kg every minute for up to 14 minutes, pre- and one-month post peripheral revascularization procedure. Exercise was terminated when patients self-reported moderate calf muscle pain (i.e., claudication). SmO₂ was measured continuously from the anteromedial aspect of the gastrocnemius muscle belly, while heart rate and blood pressure were measured beat-by-beat. Results: Reductions in SmO₂ from baseline to the 1.5 kg stage were attenuated post-revascularization when compared to pre-intervention ($-6.5 \pm 6.2\%$ vs. $-39.8 \pm 22.5\%$, $P < .05$). The change in mean arterial blood pressure was reduced post-revascularization (4 ± 4 mmHg vs. 16 ± 12 mmHg $P < .05$). PAD patients exercised longer post-revascularization (5.8 ± 0.4 min vs. 4.0 ± 1.5 min $P < .05$). Conclusions: These data suggest that revascularization reverses the rapid decline in SmO₂ during exercise, reduced the heart rate response, and may partially attenuate the blood pressure response in patients with PAD.

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Dedication

I would like to dedicate this project to my late father, Dr. Jerry C. Luck Jr., who has had a tremendous impact on my fascination with the cardiovascular system and who has inspired me to want to teach these concepts to others. Thank you for being an outstanding role model, a caring father, a loving husband, and for a life dedicated to teaching and patient care. May your kind heart and clever intellect live on in the memories of the many lives that you impacted.

Table of Contents

Abstract.....	iv
Acknowledgments.....	vi
Dedication.....	vii
Table of Contents.....	viii
Chapter 1.....	1
Introduction.....	1
Statement of the Problem.....	5
Purpose of the Study.....	6
Justification for the Study.....	6
Assumptions and Limitations.....	7
Hypotheses.....	8
Definition of Terms.....	8
Chapter 2.....	10
Review of the Literature.....	10
Epidemiology.....	10
Pathophysiology.....	11
Diagnosis.....	13
Functional Disability.....	16
Treatment.....	18

The Exercise Pressor Reflex	22
Skeletal Muscle Oxygen Saturation in Peripheral Artery Disease	23
Chapter 3.....	26
Methods.....	26
Participants.....	26
Experimental Design and Measures.....	27
Experimental Visit 1	29
Experimental Visit 2	29
Data Collection and Statistical Analysis.....	30
Chapter 4.....	31
Results.....	31
Chapter 5.....	36
Discussion.....	36
Effect of Revascularization on Skeletal Muscle Oxygen Saturation	36
Effects of Revascularization on the Exercise Pressor Reflex	37
Limitations	37
Conclusions.....	38
References.....	39
Vita.....	68

Chapter 1

Introduction

Peripheral artery disease (PAD) is classically defined as atherosclerosis of large conduit arteries that supply the lower extremity (Hirsch et al., 2001). It is a chronic, progressive, and debilitating disease reported to affect nearly 8 – 12 million Americans (Allison et al., 2007; Falk, 2006; Hiatt et al., 2008; Hirsch et al., 2001; Selvin & Erlinger, 2004). Leg blood flow is reduced in PAD as a consequence of diseased arteries that become narrowed by plaque formation in the arterial wall. The reduction in blood flow is particularly problematic during periods when the metabolic demands of active skeletal muscle outweigh the ability of the vasculature to supply blood. As a result, PAD patients may experience localized cramping leg pain with physical exertion. Leg pain that is induced by physical activity and is alleviated with rest is termed “intermittent claudication.” In many PAD patients, claudication may occur during light ambulation (i.e., walking or climbing stairs) and is associated with significant reductions in functional ability and quality of life (Hernandez et al., 2019).

Treatment options for individuals diagnosed with PAD are surprisingly few compared to other forms of cardiovascular disease. Aggressive risk factor modification (especially smoking cessation) and management of comorbidities, including hypertension, diabetes, and dyslipidemia, are appropriate for the initial management of PAD. There are few pharmacological treatments. Only two medications, cilostazol and pentoxifylline, are approved for treating claudication with cilostazol being the more effective of the two (Dawson et al., 2000). Other treatments include drugs that reduce the risk of cardiovascular events such as anti-platelets and statins. Recently, national coverage for supervised exercise therapy in patients with PAD has been approved for Medicare beneficiaries and has proven to be one of

the more promising treatment options in PAD management (Treat-Jacobson et al., 2019). Surgical bypass and catheter-based endovascular revascularization procedures (Figure 1) are typically reserved for patients with moderate-to-severe symptoms and functional impairments.

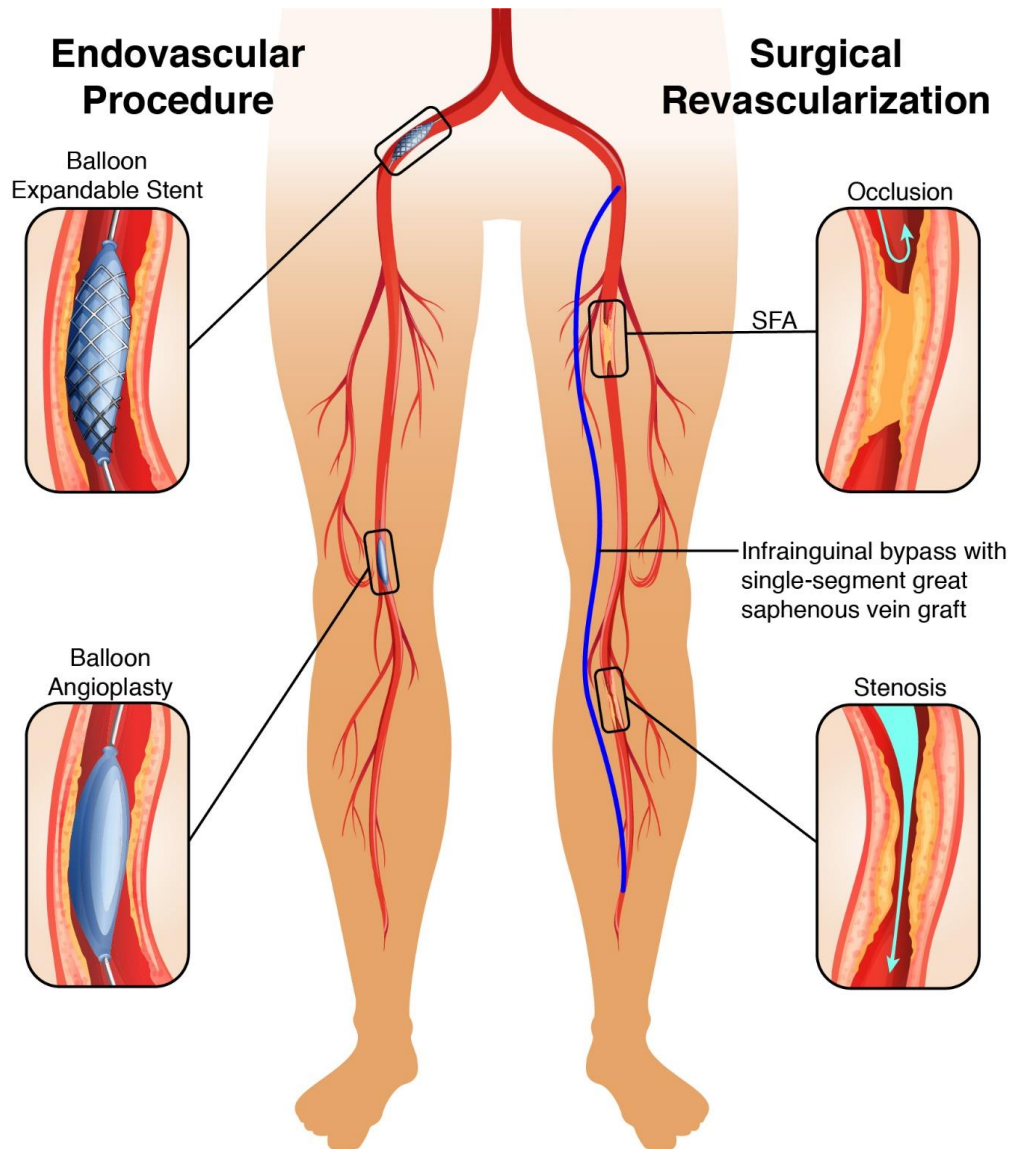


Figure 1. Endovascular and surgical revascularization for the treatment of peripheral artery disease.

Recently, peripheral revascularization procedures, that are the standard of care for the restoration of blood flow to the leg, are increasing in frequency for the treatment of symptomatic PAD (Creswell & Abelson, 2015). Between the years 1980 and 2000, Anderson and colleagues reported a 500-fold increase in all catheter-based interventions for treating peripheral atherosclerosis (P. L. Anderson et al., 2004). While the oxygen supply-demand mismatch is addressed with peripheral revascularization, the procedure does not fully normalize exercise capacity or abolish symptoms in all patients (Regensteiner, Hargarten, Rutherford, & Hiatt, 1993). However, in some individuals, revascularization could improve the cardiovascular response to exercise. It is a well-established observation that patients with PAD have an exaggerated blood pressure response to exercise when compared to healthy individuals (Baccelli et al., 1999; Bakke, Hisdal, Jorgensen, Kroese, & Strandén, 2007; Luck et al., 2017; Miller et al., 2018; Miller et al., 2017; Muller et al., 2012; Muller et al., 2015; Reggiani et al., 1999), and this relativity is associated with a greater cardiovascular disease risk (de et al., 2008). The augmented blood pressure response is likely attributed to an engagement of the exercise pressor reflex. The exercise pressor reflex is a sensory feedback mechanism, originating in the contracting skeletal muscle, that serves to modulate cardiorespiratory adjustments to meet the metabolic demands of exercise (Michelini & Stern, 2009; Mitchell, 2012). The EPR is comprised of two sensory components, specifically the muscle mechanoreflex and muscle metaboreflex (Boushel, 2010; McCloskey & Mitchell, 1972; Mitchell, Kaufman, & Iwamoto, 1983). Mechanically and chemically sensitive receptors in contracting skeletal muscle stimulate thinly myelinated group III afferents and unmyelinated group IV afferents that evoke the EPR (Kaufman, Longhurst, Rybicki, Wallach, & Mitchell, 1983; Kaufman, Rybicki, Waldrop, & Ordway, 1984). This exercise-induced increase in

sensory nerve activity stimulates cardiovascular control areas in the brainstem that increase sympathetic nerve activity and decrease parasympathetic nerve activity. This reflex is a necessary component for redirecting blood flow to active skeletal muscle. Although it has not been explicitly shown in PAD, it is unlikely that the exaggerated exercise pressor reflex is sufficient to overcome the occlusive disease during moderate to vigorous exercise (Miller et al., 2017).

As PAD is a blood flow limiting disease, it is not surprising that during exercise patients have a greater reduction in calf muscle oxygen saturation (SmO_2) compared to healthy individuals (Gardner et al., 2019; Luck et al., 2017; McCully, Halber, & Posner, 1994; Miller et al., 2017). SmO_2 is assessed by non-invasive near-infrared spectroscopy (NIRS). NIRS is a technique that utilizes the light absorbing properties of oxygenated hemoglobin (O_2Hb), deoxygenated hemoglobin (HHb), and myoglobin, to assess local oxygenation in a superficial skeletal muscle. Light that is emitted from the NIRS monitor penetrates skeletal muscle and is absorbed by varying concentrations of HbO_2 and HHb . Changes in these concentrations can be detected during exercise and quantified based on the known absorptive properties of hemoglobin (Figure 2). Exercise-induced reductions in SmO_2 , that are indicative of supply-demand imbalances in the microvasculature of active skeletal muscle, appear to accompany the exaggerated exercise pressor reflex in PAD (Luck et al., 2017; Miller et al., 2017). A previous study in our laboratory showed that revascularization improves the blood pressure responses to dynamic foot exercise (Miller et al., 2018). It is suspected that increased perfusion to the exercising skeletal muscle attenuates the exercise pressor reflex in PAD. However, this has not been explicitly tested. The present study is designed to evaluate whether peripheral

revascularization (endovascular or surgical) reverses the rapid decline in active muscle SmO_2 during plantar flexion exercise, as well as reduce the accentuated EPR in PAD.

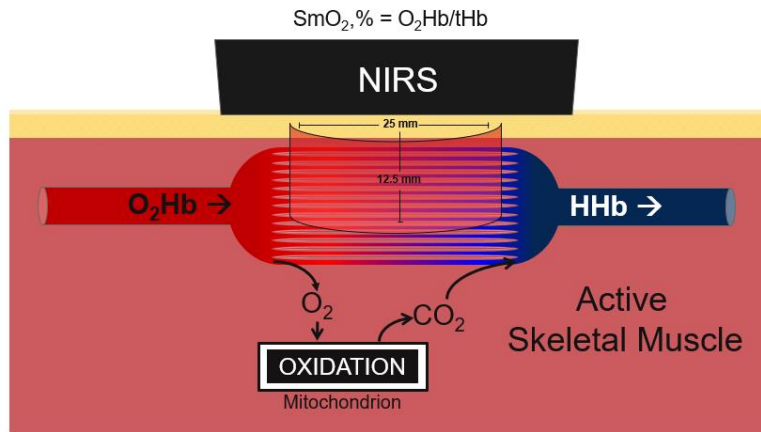


Figure 2. A basic schematic representation of a near-infrared spectroscopy (NIRS) monitor. Light is injected into a superficial skeletal muscle from a light emitting diode and is detected by a photodetector. The penetration depth is roughly one-half the distance between the light emitter and the detector. Oxygenated hemoglobin (O_2Hb) and deoxygenated hemoglobin (HHb) have different light absorptive properties allowing for the measurement of muscle oxygen saturation (SmO_2). SmO_2 is the ratio of O_2Hb and total hemoglobin (tHb) expressed as a percentage.

Statement of the Problem

The problem of the study is that it remains to be fully elucidated as to what degree the restoration of blood flow (via peripheral revascularization) improves active skeletal muscle oxygenation or reduces the augmented exercise pressor reflex in PAD.

Purpose of the Study

The purpose of the study is to examine whether 1.) leg revascularization increases calf muscle SmO₂ during foot exercise and 2.) whether the peripheral revascularization reduces the exaggerated exercise pressor reflex in patients with symptomatic PAD.

Justification for the Study

Peripheral revascularization procedures are performed to treat symptomatic PAD with the objective of improving perfusion to the tissues of the lower extremity. A procedure is considered “successful” with an improvement in the systolic ankle-to-brachial index (ABI >0.15) (M. M. McDermott et al., 2013). An ABI \leq 0.90 is indicative of occlusive disease in the arteries supplying the lower extremity, where a lower ABI value is predictive of greater severity (Gardner & Afaq, 2008). However, these procedures do not reverse atherosclerotic disease as they do not alter the underlying pathogenic mechanisms. Restenosis or recurrent occlusions are the leading complication following peripheral revascularization (de Donato et al., 2017; Setacci et al., 2012) and symptoms may persist in many patients (T. W. Rooke et al., 2011). While emerging research indicates that the pathophysiology of PAD is far more complex than simply reductions in blood flow (Stewart, Hiatt, Regensteiner, & Hirsch, 2002), it is the general consensus that the chronic occlusive disease initiates abnormalities in the skeletal muscle. Recent work has shown that restoring blood flow via revascularization may slow the progression of fibrosis and scarring in the skeletal muscle (Ha et al., 2016). However, it is not fully understood why some patients continue to experience symptoms following these endovascular and surgical interventions that improve or sometimes normalize the ABI. It is also important to note that while walking ability tends to improve following revascularization

(Fakhry, Spronk, van der Laan, & et al., 2015), functionality certainly is not restored to normal levels in most patients.

Mismatches in O₂ supply and demand compromise oxidative metabolism in active skeletal muscle and can be easily and noninvasively monitored using near-infrared spectroscopy (NIRS). NIRS has been previously used to measure oxygenation responses within exercising leg muscles in PAD patients (Bauer, Brass, Barstow, & Hiatt, 2007; Beckitt, Day, Morgan, & Lamont, 2012; Luck et al., 2017; McCully et al., 1994; McCully, Landsberg, Suarez, Hofmann, & Posner, 1997). Previous studies have shown that reductions in active muscle SmO₂ are greater in patients with PAD (Bauer et al., 2007; Bauer, Brass, & Hiatt, 2004; Luck et al., 2017; Miller et al., 2017). Recent work in our lab has shown that the blood pressure response to exercise is attenuated one-month post revascularization (Miller et al., 2018). However, to what extent the altered blood pressure response is associated with improvements in SmO₂ remains unclear.

Assumptions and Limitations

Interpretations of the results from the present study considered the following assumptions and limitations:

1. There was no control group.
2. The physiological calibration for the NIRS device could not be performed because it could potentially compromise the integrity of the implanted stent in the leg; thus, comparing the absolute values to other NIRS devices is not recommended.
3. The changes in patient's medications (i.e., the addition of anti-platelet therapies to reduce cardiovascular events) may have influenced these results.

4. The NIRS device assumes that the sample volume is 100% homogeneous. However, skeletal muscle biopsies were not obtained in the present study and thus it is not known if PAD patients had significant intramuscular fat or fibrosis that might have attenuated the NIRS signal.
5. Intracellular myoglobin is similar in structure to hemoglobin and thus it is difficult to discern its contribution in the NIRS signal.
6. The assumption that the muscle oxygen saturation can be altered with low-intensity incremental supine plantar flexion exercise in PAD.
7. The assumption that occlusive disease reduced blood flow to the medial gastrocnemius muscle to the same extent in all PAD patients.

Hypotheses

The study tested the following hypotheses:

1. Revascularization will reduce the large drop in skeletal muscle oxygen saturation in PAD during graded plantar flexion exercise.
2. The revascularization of blood flow will significantly reduce the exaggerated exercise pressor reflex observed in PAD.

Definition of Terms

Skeletal muscle oxygen saturation (SmO_2). The ratio of oxygenated hemoglobin (O_2Hb) concentration to total hemoglobin (tHb) concentration expressed as a percent ($SmO_2 = O_2Hb/tHb$) (Schmitz, 2015). As shown in Figure 2, SmO_2 is quantified non-invasively via a technique called near-infrared spectroscopy (NIRS).

Fatigue. The time point where plantar flexion exercise was terminated at the pre-revascularization visit. Each subject's post-revascularization data was then time matched to their previous visit fatigue time point. However, subjects may exercise beyond their fatigue point determined at the pre-revascularization visit. If this is the case, the time point will be referred to as "end exercise."

Chapter 2

Review of the Literature

Epidemiology

The most recent estimates suggest that 8 to 12 million people in the United States and 200 million people worldwide are affected by PAD (Allison et al., 2007; Falk, 2006; Hiatt, Armstrong, Larson, & Brass, 2015; Hiatt et al., 2008; Hirsch et al., 2001; Patel et al., 2015; Selvin & Erlinger, 2004). The prevalence of PAD is reported to be greater in men (Hirsch et al., 2012; Hirsch et al., 2006; Norgren et al., 2007). However, in patients above the age of 85, there is a shift in prevalence as PAD becomes more common in women (Diehm et al., 2004; Hirsch et al., 2012). The estimated prevalence of PAD is determined by the systolic ankle-to-brachial index (ABI) screening (see *Diagnosing PAD*, p. 11). Abnormal ABIs are detected in roughly 6% of people over 40 years old and 20% of people over the age of 65 (Pande, Perlstein, Beckman, & Creager, 2011).

As PAD is a manifestation of systemic atherosclerosis, it is not surprising that patients with the disease have an increased risk of thromboembolic events (e.g., myocardial infarctions and cerebral vascular accidents) as well as an increase in all-cause mortality (Ouriel, 2001); the likelihood of patients dying over the next 10 years is three times greater when compared to healthy individuals (Criqui et al., 1992). Furthermore, mortality as a consequence of coronary artery disease affects over half of the patients with PAD (Dormandy & Rutherford, 2000). Although, as treatments continue to improve, it is possible that other diseases like cancer will become the leading cause of death in this population.

Risk factors for PAD include cigarette smoking, diabetes mellitus, increased age, hypertension, hypercholesterolemia, Hyperhomocysteinemia, chronic kidney disease, insulin

resistance, and increased C-reactive protein levels (Criqui & Aboyans, 2015; Guallar et al., 2006; Muller, Reed, Leuenberger, & Sinoway, 2013; O'Hare, Glidden, Fox, & Hsu, 2004; Pande, Perlstein, Beckman, & Creager, 2008; Selvin & Erlinger, 2004). Individuals who smoke significantly increase their risk of developing PAD, while risk decreases following the cessation of smoking (Criqui & Aboyans, 2015). Diabetes increases the risk of developing PAD (Marso & Hiatt, 2006). In PAD patients with diabetes and/or those that smoke show an increased risk of developing critical limb ischemia (a consequence of PAD that typically requires amputation of necrotic tissue or gangrene) (Beckman, Paneni, Cosentino, & Creager, 2013). These same risk factors are also highly associated with coronary atherosclerosis and other forms of cardiovascular disease. Thus, aggressive management of risk factors is important when treating PAD.

Pathophysiology

PAD is atherosclerosis that affects the conduit arteries of the lower extremity (Hiatt, Hoag, & Hamman, 1995). Atherosclerosis is a chronic systemic inflammatory disease (Mullenix, Andersen, & Starnes, 2005) where arteries become progressively blocked by fibrofatty plaque deposits (Falk, 2006). This process is slow to develop and effectively reduces arterial blood supply to distal regions (i.e., skeletal muscles in the lower extremity). In most cases at rest, O₂ supply satisfies O₂ consumption. However, increases in metabolic demand (i.e., during walking exercise) result in O₂ supply-demand mismatches. During these periods of limited O₂ supply, exercising skeletal muscle becomes ischemic and some patients may develop walking leg pain, termed “intermittent claudication.” Exertional leg pain may occur in the buttocks, thigh, or calf region. This pain is alleviated by rest, allowing the return of blood flow to replenish the metabolic deficit. The etiology of the walking leg pain can be described

similarly to the way blockages of the coronary arteries result in angina. However, these hallmark symptoms (i.e., intermittent claudication) present in roughly 10% to 35% of patients, while 40% to 50% of patients present with atypical leg pain and the remaining 40% to 50% are asymptomatic (Hirsch et al., 2001; Hirsch et al., 2007; M. M. McDermott et al., 2001). Due to this nonspecific presentation, PAD has often been regarded as the most common form of cardiovascular disease that is most commonly underdiagnosed (Belch et al., 2003; Diehm et al., 2006; Hirsch et al., 2006; Rosero, Kane, Clagett, & Timaran, 2010).

Patients with PAD have increased vascular resistance. This increase is a result of a stenosis reducing blood flow. However, endothelial dysfunction and impaired vasodilation also contribute to the increase in total peripheral resistance. Reductions in flow can be described by the Poiseuille equation:

$$Q = \frac{\Delta P \pi r^4}{8 \eta l}$$

where (Q) is blood flow, (ΔP) is the change in pressure gradient across the stenosis, (r) is the radius of the lumen, (η) is the blood viscosity, and (l) is the length (Badeer, 2001). Changes in vessel radius have a tremendous impact on flow. As the radius decreases, so too does flow. There is also a large pressure gradient that develops across stenotic lesions. With exercise, metabolic byproducts build up in the active tissue distal to the stenosis and promote local vasodilation. While blood flow is typically enhanced with vasodilation, the atherosclerotic plaque reducing the diameter of the arterial lumen ultimately dictates the amount of blood flow to distal regions. This vasodilation with a lack of blood flow could effectively lower perfusion pressure and worsen O_2 kinetics. If the stenosis is small, there may be little disruption in flow, as the formation of collateral vessels help to promote blood flow past diseased areas (Coats & Wadsworth, 2005). However, in more severe cases, even collateral development cannot

overcome these obstructions. Often, the arterial system that feeds the collateral system can also become diseased causing further reductions in blood flow.

Over time, PAD patients experience repetitive bouts of ischemia in the legs and develop skeletal muscle myopathy, microcirculatory, and mitochondrial dysfunction (Harwood, Cayton, Sarvanandan, Lane, & Chetter, 2016; Hiatt et al., 2015; Pipinos et al., 2007, 2008; Robbins et al., 2011). It has been shown that PAD patients suffer from a nearly tenfold greater decline of skeletal muscle mass (i.e., sarcopenia) when compared to healthy controls (Addison et al., 2018). Other pathological changes include reductions in capillary density, type 1 fibers, electron transport enzymes, the rate of phosphocreatine recovery after exercise, increases in lactate accumulation at low workloads, and abnormalities in the utilization of oxygen in active skeletal muscle (J. D. Anderson et al., 2009; Bauer, Brass, & Hiatt, 2004; Bauer, Brass, Nehler, Barstow, & Hiatt, 2004; Brass & Hiatt, 2000; Brass, Hiatt, Gardner, & Hoppel, 2001; Frisbee, Wu, Goodwill, Butcher, & Beard, 2011; Isbell et al., 2006; Pipinos, Shepard, Anagnostopoulos, Katsamouris, & Boska, 2000; Robbins et al., 2011). Together, these factors likely contribute to the walking impairment in PAD.

Diagnosis

There are several ways to diagnose PAD, however, the ambiguity in symptomology make this more difficult than other forms of cardiovascular disease. Questionnaires are used to gauge PAD symptoms and walking ability. The Rose questionnaire, The San Diego Claudication Questionnaire, and the Walking Impairment Questionnaire are all or partially PAD specific questionnaires commonly used to assess symptoms and level of impairment (Criqui & Aboyans, 2015; Criqui et al., 1996; Regensteiner, 1990; Rose, 1962). Patients may also present with physical findings such as skin atrophy and atypical hair loss on the legs

(Sontheimer, 2006). Apart from the history and physical examination, the ABI is typically the first test used to diagnose PAD. The test is easy to perform and cost effective. The ABI was first described by Winsor T. in 1950 and has since become the norm in noninvasively diagnosing PAD (Winsor, 1950; Yao, Hobbs, & Irvine, 1969). The ABI consists of bilateral BP measurements taken at the ankle (posterior tibial or dorsalis pedis artery) and brachial artery in the supine posture. The measurement is calculated by dividing the highest pressure in the ankle/foot by the highest pressure in the upper extremity. ABIs have been reported in the seated position, however, a correction factor must be applied (Gornik et al., 2008). According to the PAD guidelines from the American College of Cardiology and the American Heart Association, a normal ABI is 1.00 to 1.40 (Thom W. Rooke et al., 2011). ABI values above 1.40 are indicative of calcified arteries. An ABI of 0.91 to 0.99 is considered borderline, while an ABI below 0.90 is considered abnormal (i.e., suggestive of atherosclerotic obstruction) (Thom W. Rooke et al., 2011). In general, lower ABI values indicate a more severe level of disease and a lower five-year survival rate (Resnick et al., 2004; T. W. Rooke et al., 2011). Patients with classic symptoms of intermittent claudication may present with an ABI in the range of 0.50 to 0.80. An ABI below 0.50 is often associated with critical limb ischemia caused by severe arterial insufficiency. Critical limb ischemia involves chronic ischemic rest pain, ulceration, and/or the development of gangrene (Norgren et al., 2007; Varu, Hogg, & Kibbe, 2010), and if left untreated, critical limb ischemia typically results in the loss of limb. However, it is important to note that critical limb ischemia is considerably rare (occurring in only 1% to 2% of the PAD population) (Hirsch et al., 2001; Hirsch et al., 2006). The ABI is a relatively quick objective assessment and has a specificity (83% – 99%) and sensitivity (69% – 73%) for the detection of stenotic lesions over 50% (Thom W. Rooke et al., 2011). The test can detect

PAD even in the absence of leg pain or classic symptoms. In fact, relying primarily on classic claudication symptoms could fail to detect most patients with PAD, while the ABI is more closely correlated to reductions in leg function (M. M. McDermott et al., 2002). It is important to note that PAD patients have a reduced ABI following walking exercise. Gardner and colleagues demonstrated that following graded treadmill exercise, the ABIs in PAD patients were lower for up to 10 minutes post exercise (Gardner, Skinner, Cantwell, & Smith, 1991). Thus, it is reasonable to use exercise testing to help confirm a diagnosis of PAD in patients where exercise testing is not contraindicated. Exercise tests, such as the six-minute walking test (6MW) and progressive treadmill tests (Gardner et al., 1991), are commonly used to identify claudication onset time (COT), peak walking time (PWT), and peak walking distance (PWD). A patient with PAD will have reductions in these specific outcome measures and thus, will have impaired functional ability and increased morbidity and mortality (Criqui et al., 1992). Exercise testing is also a useful tool to differentiate between disease progression and functional impacts.

Other tests (segmental pressures, toe-brachial index, pulse volume recording, Doppler imaging, transcutaneous oxygen monitoring, and angiography) are used to identify the location and severity of the disease. A segmental pressure measurement uses a series of blood pressure cuffs placed at various levels on the leg. A reduction in pressure greater than 20 mmHg in the sequential segment is indicative of disease. Also, segmental pressure differences between legs greater than 30 mmHg is also considered indicative of PAD (Hirsch et al., 2006). The toe-brachial index (TBI) is similar to the ABI where a value less than 0.6 is indicative of PAD (Ramsey, Manke, & Sumner, 1983). Pulse volume recordings use the same pressure cuff setup as segmental pressures to obtain pulsatile volume changes in the legs. Decreases in pulse

volume amplitude and an absent dicrotic notch are considered abnormal (Darling, Raines, Brener, & Austen, 1972; Kempczinski, 1982). Doppler imaging uses ultrasonography to detect blood flow in arteries. Typically, the normal doppler waveform is triphasic with a prominent upward systolic peak followed by a slightly negative early diastolic wave and then a slightly positive late diastolic wave. In the presence of PAD, doppler waveforms are biphasic or monophasic (Sibley et al., 2017). An additional non-invasive measure is transcutaneous oxygen monitoring (TcPO₂) which is useful for the assessment of severe ischemia (Cao et al., 2011; Gerhard-Herman et al., 2017). Catheter-based imaging techniques, called angiography, are also used to identify the location and severity of the disease. These endovascular procedures are invasive and require the injection of contrast dye into the arterial system. Angiograms are typically performed to assist in the decision for treating patients with more aggressive endovascular or surgical procedures.

Functional Disability

It is important to note that patients with PAD (even those that are asymptomatic) experience functional decline (Mary McGrae McDermott, 2015; M. M. McDermott et al., 2010; M. M. McDermott, Fried, Simonsick, Ling, & Guralnik, 2000; M. M. McDermott et al., 2002). Many patients may develop exercise intolerance (Askew et al., 2005; M. M. McDermott et al., 2002) that can impact activities of daily living and significantly exacerbate the progression of the disease (Regensteiner, Wolfel, et al., 1993). Patients with PAD develop functional decline secondary to atherosclerotic vascular obstruction(s). Functional disability includes walking impairment (i.e., inability to walk six minutes without stopping, reduced treadmill walking time, and an inability to climb stairs). The 6-minute walk distances have been extensively reported over the years in both healthy populations as well as in PAD

(Addison et al., 2018; Camarri, Eastwood, Cecins, Thompson, & Jenkins, 2006; Casanova et al., 2011; M. M. McDermott et al., 2011). These functional declines are greater and more rapid in PAD compared to healthy persons without atherosclerotic disease (M. M. McDermott et al., 2010; M. M. McDermott et al., 2000; M. M. McDermott et al., 2002; M. M. McDermott et al., 2001; M. M. McDermott et al., 2009; M. M. McDermott et al., 2004). Women with PAD have been shown to experience faster functional decline than men, thought to be caused by reduced muscle mass at baseline (M. M. McDermott et al., 2011). In addition to reductions in physical activity correlating with increased mortality and cardiac events (Garg et al., 2006), PAD patients have a reduced quality of life and an increased incidence of depression (Regensteiner et al., 2008; Smolderen et al., 2009).

In general, patients with lower ABIs have greater functional impairment and have to stop more frequently during walking exercise (M. M. McDermott et al., 2002). However, most patients with PAD do not experience the classical symptoms (i.e., intermittent claudication) (Hirsch et al., 2007; Mary McGrae McDermott, 2015; M. M. McDermott et al., 2001). In fact, in the Rotterdam Study, of the subjects with abnormal ABIs (i.e., < 0.90), only 6.3% experienced intermittent claudication (Meijer et al., 1998). It is unclear whether physical inactivity contributes to atypical symptomology. In other words, some PAD patients who are not active enough to elicit symptoms, may not seek out their healthcare provider.

Recent studies suggest that slow gait speed (i.e., ≤ 0.8 m/s) and gait mechanics are associated with poor health outcomes in PAD (Gardner, Forrester, & Smith, 2001). The Gardner treadmill protocol is commonly used to assess the severity of functional walking impairment in PAD (Gardner et al., 1991). The protocol consists of treadmill walking at a constant speed of 2 miles per hour (0.89 m/s). Starting at a grade of 0%, the grade is increased

by 2% every 2 minutes until fatigue. Patients rate their level discomfort every minute via a zero to four scale (0 = no discomfort, 1 = onset of discomfort, 2 = moderate discomfort, 3 = severe discomfort, 4 = maximal discomfort). Claudication onset time (COT) is defined as the walking time before the onset of leg discomfort (i.e., 1 on the discomfort scale). Patients are instructed to walk until maximal discomfort (i.e., 4 on the discomfort scale). Peak walking time (PWT) is defined as the total walking time of the protocol. While treadmill testing confirms the degree of functional decline in PAD, it requires longer time, equipment, and personnel to conduct accurate screening protocols.

Treatment

While developments have been made in stent design, when compared to other forms of cardiovascular disease, there are limited treatment options for PAD patients. Treatment options include management of risk factors, pharmacological management to lower the risk of cardiac events and reduce symptoms, endovascular and surgical revascularization procedures to restore or improved blood flow to the leg(s), and exercise therapy.

Initial treatment begins with modifications of risk factors, including smoking, diabetes mellitus, hypertension, and dyslipidemia. As smoking is the largest contributing risk factor, all patients are strongly encouraged to quit when diagnosed with PAD. Medications are prescribed to help control other risk factors. Patients will typically be prescribed an anti-platelet medication (i.e., acetylsalicylic acid or clopidogrel), statins, and possibly cilostazol. Cilostazol is one of two phosphodiesterase type three inhibitors that are approved by the Food and Drug Administration (FDA) for the treatment of claudication in PAD. The other FDA approved drug, Pentoxifylline, is typically not prescribed as it has been shown that it is no more effective than placebo in improving maximum walking distance (Dawson et al., 2000).

Revascularization procedures can be done endovascularly or surgically to reestablish blood flow (see figure 1). Endovascular revascularization is a catheter-based approach that consists of angioplasty, stenting, or atherectomy. These procedures are considered minimally invasive. Balloon angioplasty was first described by Dotter and Judkins (Dotter & Judkins, 1964) and involves placing a deflated balloon into the artery via a percutaneous transluminal catheter. The deflated balloon is advanced over a guidewire to the level of the stenosis and dilated. The dilated balloon forces open hardened plaque in the vessel wall and increases the vessel lumen diameter thus improving blood flow to the distal vasculature. Patency with angioplasty is greatest in the aortoiliac region and gradually decreases in the distal vasculature (Norgren et al., 2007). However, balloon angioplasty is less effective at treating long and more complex lesions when compared to stents (Mewissen, 2009). A stent is a metal structure that can be placed on a balloon catheter and expanded in areas of stenosis. The placement of a stent can help to open the vessel lumen and improve patency (Vogel, Shindelman, Nackman, & Graham, 2003). However, stents placed in the lower extremity can be subjected to high mechanical stress from movement (e.g., bending of the hip and knee joints). Stent placement is also avoided in the common femoral artery as it can interfere with arterial access during future interventions (Kullo & Rooke, 2016). Thus, lesions in the common femoral artery are often treated surgically using endarterectomy (Farber, 2018). Atherectomy is an endovascular procedure that cuts or shaves atherosclerotic plaques and removes them from vessel walls effectively increasing lumen size (Bhat, Afari, & Garcia, 2017) although it is unclear whether this technique outperforms balloon angioplasty or stents (Ambler, Radwan, Hayes, & Twine, 2014). Surgical revascularization procedures (e.g., bypass or endarterectomy) are typically reserved for patients where endovascular revascularization is not possible or previous

interventions have failed (Kullo & Rooke, 2016). These procedures are invasive and are generally associated with greater risk, however, surgical bypass is associated with high patency (Chiu, Davies, Nightingale, Bradbury, & Adam, 2010). Bypass can be accomplished by using prosthetic grafts or a vein graft, typically made with the great saphenous vein. Bypass is an aggressive treatment option for patients with symptomatic PAD; however, it is generally the standard for patients suffering from critical limb ischemia (Gardner & Afaq, 2008). The goal of both surgical and endovascular revascularization is to improve blood flow and reduce the incidence of tissue loss that may require amputation. While symptoms are often improved with these procedures, they do not entirely improve function in all patients (Oresanya et al., 2015). A large collection of evidence supports the use of exercise therapy, either alone or in addition to the treatment options previously described, for optimal improvements in functionality (Treat-Jacobson et al., 2019).

The addition of supervised exercise training (SET) is arguably the largest change in the management of PAD in recent years (Jensen, Chin, Ashby, Schafer, & Dolan, 2017; M. M. McDermott, 2018; Treat-Jacobson et al., 2019). Medical insurance coverage includes 12-week/36 sessions that recommend walking based exercise be done at least three times per week, for at least a total of 30 minutes a day. SET is to be done in a healthcare setting and under the supervision of a physician. Currently, the American College of Sports Medicine (ACSM) recommends supervised exercise training consists of aerobic exercise (e.g., free or treadmill walking) to the point of moderate pain on the claudication pain scale (Treat-Jacobson, Henly, Bronas, Leon, & Henly, 2011) for three to five days per week. The duration of exercise bouts may vary based on disease severity; however, a total of 30-45 minutes per week (excluding periods of rest) and may progress to 60 minutes a day or more (American College

of Sports, Riebe, Ehrman, Liguori, & Magal, 2018). Resistance exercise may be recommended for patients with PAD (American College of Sports et al., 2018) as patients develop muscle myopathy and suffer from reductions in lower extremity muscle mass. However, resistance exercise training is not as beneficial as aerobic exercise training for improving 6-minute walk distance in PAD (Mary M. McDermott et al., 2009).

The evidence for benefits of SET in PAD is vast and dates back to the 1960's (Larsen & Lassen, 1966). Recent studies by Gardner and colleagues suggest that both SET and homebased exercise training is beneficial in PAD (Gardner, Parker, Montgomery, & Blevins, 2014; Gardner, Parker, Montgomery, Scott, & Blevins, 2011). In an early study by Lundgren and colleagues, a randomized comparison between SET, revascularization, and SET plus revascularization in 75 PAD patients showed that walking function improved across all three groups. However, walking performance was significantly greater in patients that underwent revascularization plus SET (Lundgren, Dahllof, Lundholm, Schersten, & Volkmann, 1989). Since Lundgren's initial study, several other studies indicated that revascularization plus SET showed favorable results for improving walking function (Creasy, McMillan, Fletcher, Collin, & Morris, 1990; Mazari et al., 2010; Mazari et al., 2012). In one large trial involving 212 PAD patients, those that underwent SET plus endovascular revascularization had a longer peak walking distance when compared to individuals that received only SET (Fakhry et al., 2015). However, one study by Gelin et al has shown that walking ability improved in the revascularized group compared to SET. The CLEVER study showed that SET and stenting improved peak walking time over optimal medical care in 111 PAD patients (T. P. Murphy et al., 2012; Timothy P Murphy et al., 2015). These data suggest that both revascularization and SET improves walking performance. Moreover, SET may be just as effective as endovascular

interventions for improving walking performance, and when done in conjunction, their effects appear to complement one another.

The Exercise Pressor Reflex

While exercise therapy and increased activity is clearly beneficial for PAD patients, it is important to note that these individuals have an abnormal cardiovascular response to exercise. A reduction in blood flow to exercising skeletal muscle has been shown to activate a sympathoexcitatory pathway, termed the exercise pressor reflex (EPR) (Alam & Smirk, 1937; Augustyniak, Ansoorge, & O'Leary, 2000; Kaur et al., 2015). This phenomenon was first observed in the 1930's when Alam and Smirk used various techniques to occlude the circulation in exercising legs and forearms. The study showed reflex increases in BP and HR post exercise while the limb was left occluded. The study was the first to suggest that there was a neural component to the reflex because circulating metabolites were confined to the occluded limb. The neural control of the circulation has since been extensively expanded on by others (Coote, Hilton, & Perez - Gonzalez, 1971; Goodwin, McCloskey, & Mitchell, 1971; McCloskey & Mitchell, 1972). In animal studies, it was discovered that when stimulated by muscle contraction, thin fiber muscle afferents (i.e., groups III and IV) evoked the exercise pressor reflex (Kaufman et al., 1983). From here, Kaufman and others have described the functional properties of group III (mechanoreceptors) and group IV (metaboreceptors) muscle afferents and their involvement in the EPR (Ellaway, Murphy, & Tripathi, 1982; Kaufman et al., 1983; Kaufman et al., 1984; Kenagy, VanCleave, Pazdernik, & Orr, 1997; Kumazawa & Mizumura, 1977; Mense & Stahnke, 1983; Paintal, 1960; Sinoway, Hill, Pickar, & Kaufman, 1993). It has been concluded that the exercise pressor reflex serves as a feedback mechanism, arising from the contracting skeletal muscle, that increases the cardiovascular response to meet

the metabolic demands of exercise (Stone & Kaufman, 2015). Animal models of PAD using femoral artery ligation have been used to show the activation of the EPR in reductions of blood flow to skeletal muscle (Waters, Terjung, Peters, & Annex, 2004). However, large artery hemodynamics do not fully explain symptomology in PAD patients (Brass, Hiatt, & Green, 2004; Gardner, Skinner, Cantwell, & Smith, 1992). Nevertheless, the rise in arterial BP is related to an increased risk of adverse cardiovascular events in patients with PAD (de et al., 2008; Lewis et al., 2008; Weiss, Blumenthal, Sharrett, Redberg, & Mora, 2010).

Skeletal Muscle Oxygen Saturation in Peripheral Artery Disease

During aerobic exercise, oxygen supply must equal the amount of oxygen consumed by the active skeletal muscle. This relationship between the uptake of oxygen ($\dot{V}O_2$) and oxygen delivery via cardiac output (\dot{Q}) is one of the fundamental principles of exercise physiology as first described by Adolph Fick (Fick, 1870). The Fick equation is defined as:

$$\dot{V}O_2 = \dot{Q} \times (a - v\dot{O}_2 \text{ difference})$$

where $a - v O_2$ difference is the change in oxygen concentration across the microcirculation. During aerobic exercise, the $a - v O_2$ difference widens (i.e., the venous oxygen concentration falls, and the arterial oxygen concentration is normally maintained) and subsequently widens the partial pressure of oxygen gradient in the skeletal muscle and improves oxygen diffusion. As $\dot{V}O_2$ increases, so too does \dot{Q} and $a - v O_2$ difference. Whole body oxygen uptake can be measured using pulmonary metabolic gas analyzer. However, this technique does not allow for the quantification of localized skeletal muscle oxygen consumption. Other techniques that include magnetic resonance imaging or arterial/venous catheterization are expensive, invasive, or are generally not conducive for exercise studies.

Recently, NIRS has been used to assess microvascular oxygen kinetics across several muscles (Chris J McManus, Jay Collison, & Chris E Cooper, 2018). This technique was first described by Jöbsis in 1977 (Jobsis, 1977). The NIRS device provides noninvasive measures of oxygenated hemoglobin (O₂Hb), deoxygenated hemoglobin (HHb), and microcirculatory O₂ saturation where SmO₂ is the ratio of O₂Hb to total hemoglobin (tHb; tHb = O₂Hb + HHb) expressed as a percentage [SmO₂ = O₂Hb/(tHb)]. The use of NIRS in muscle O₂ kinetics has been extensively reviewed (Ferrari, Muthalib, & Quaresima, 2011; Grassi & Quaresima, 2016; Hamaoka, McCully, Niwayama, & Chance, 2011; Jones, Chiesa, Chaturvedi, & Hughes, 2016). Once the device is placed on the patient, NIRS light travels through the underlying tissue in an arcing pathway from the emitter to the detector (Figure 2). Attenuation of light is caused by the scattering of light equally in all directions as it is emitted from the light source. Light is then absorbed by O₂Hb and HHb, and to some extent myoglobin, intracellular and extracellular water, and pigment in skin. Knowing the absorptive properties and using multiple source detectors at different distances can improve and isolate muscle tissue for quantification of SmO₂. Absorbance (A) in a tissue is defined as:

$$A = \log_{10} \left(\frac{I_1}{I_0} \right)$$

Where I_1 is the transmitted light and I_0 is the source light. As more light is adsorbed by the tissue, less light is transmitted back to the detector. The absorbance of light can be explained by Beer Lambert Law:

$$A = \log_{10} \left(\frac{I_1}{I_0} \right) = \epsilon bc$$

Where ϵ is the known molecular extinction coefficient, b is the known path length, and c is the known concentration. Commercially available NIRS devices work from this principal

in that the source-detector distance is known and the extinction coefficients for O₂Hb and HHb are known. Transmitted light can be measured, and the concentrations of O₂Hb and HHb can be quantified. The device used in the present investigation utilizes a four-layer (epidermis, dermis, adipose, and muscle) Monte Carlo model. The monitor also uses one light source, a short and long-distance detector, and an algorithm in an attempt to isolate the skeletal muscle signal from the superficial skin and adipose layer. NIRS is able to track changes in skeletal muscle oxygenation during exercise (C. J. McManus, J. Collison, & C. E. Cooper, 2018) and is often used in research in patients with PAD (Bauer et al., 2007; Bauer, Brass, & Hiatt, 2004; Gardner et al., 2014; Halber, Posner, & McCully, 1994; Murrow et al., 2019). It is not known if these measures are influenced by severity of disease. For the present study, NIRS is a valuable measure to investigate the exercise response in patients treated for symptomatic PAD.

During exercise, local and systemic cardiovascular adjustments promote hyperemia in active tissue to increase the delivery of oxygen to active tissue. However, as previously stated, patients with PAD experience chronic reductions in skeletal muscle blood flow (and thus, reduced oxygenation) during dynamic exercise, as well as an exaggerated exercise pressor reflex (Baccelli et al., 1999; Bakke et al., 2007; Luck et al., 2017; Miller et al., 2018; Miller et al., 2017; Muller et al., 2012; Muller et al., 2015). The use of NIRS is a practical tool to help investigate improvements in perfusion following revascularization and whether or not it contributes to other improvements in cardiovascular function, as previously shown (Miller et al., 2018).

Chapter 3

Methods

Participants

Male and female patients with PAD (n=6) completed the present study. Subjects were preliminarily screened from the Penn State Heath vascular clinic lists or previous enrolled studies and contacted by the study coordinator/clinical research nurses. All experiments were approved in advance by the Institutional Review Boards of the Penn State Milton S. Hershey Medical Center and Appalachian State University and conformed with the Declaration of Helsinki. All subjects provided written and informed consent. All contacted patients had received a previous diagnosis of PAD (i.e., ABI < 0.9) and were scheduled for a standard-of-care vascular procedure at Penn State. PAD patients with diabetes were included if stable on their medications and showed no significant symptomatic peripheral neuropathy. PAD patients with a recent history of unstable angina or myocardial infarction (<6 months), current unstable angina or a primary symptom of angina, and/or elevated serum creatinine >2.0 mg/dl that would be indicative of renal failure were excluded. Patients were also excluded if they had signs and symptoms of severe PAD (e.g., resting leg pain or open non-healing wounds). Individual subject characteristics (age, location of arterial occlusion, height, weight, and pre- and post-revascularization ABI) are shown in Table 1. Four of the six subjects had hyperlipidemia, three had coronary artery disease, three were hypertensive, one had chronic obstructive pulmonary disease, and one had peptic ulcer disease (Table 2).

Patients underwent lower extremity revascularization procedures (Table 3). Of the six patients in the study, four received balloon angioplasty and four received stents (two received both). Two of the six patients underwent endarterectomy. Stents were placed in the common iliac artery (3/6) and in the external iliac artery (1/6). Bilateral kissing stents were placed in

the iliac arteries in one patient. Patients maintained their usual medication regimen during the study (Table 4), including clopidogrel (6/6), statins (5/6), acetylsalicylic acid (4/6), beta adrenergic receptor blockers (4/6), angiotensin-converting-enzyme inhibitors (3/6), proton pump inhibitors (2/6), bronchodilators (2/6), diuretics (2/6), multivitamins (2/6), antidepressants (1/6), calcium channel blockers (1/6), anti-diabetic medications (1/6), anticonvulsants (1/6), coenzyme Q₁₀ (1/6), and vitamin D (1/6). Subjects were taking the same medications and doses for both visits; however, three patients began antiplatelet therapy after their intervention, per the standard of care following revascularization procedures. All participants reported a previous history of smoking, and one of the six patients was currently smoking.

Experimental Design and Measures

The present study utilized a pre-experimental, pretest-posttest design where each subject served as their own control. Subjects reported to the laboratory after refraining from (i) caffeine for at least 12 hours and (ii) all over-the-counter medications, alcohol, and extreme exercise for 24 hours before the visit. The laboratory room temperature was maintained between 22 and 25 °C during all visits. After resting for several minutes, supine ABIs were measured on both the right and left side. Two continuous-wave NIRS monitors (MOXY muscle oxygen monitor; Fortiori Design, Hutchinson, MN) were attached to the right and left calf at the region of the medial gastrocnemius. Wavelengths at approximately 750 and 850 nm were used (Matcher, Cope, & Delpy, 1997). To ensure proper signal penetration depth, adipose tissue thicknesses (ATT) was obtained using ultrasound imaging (iE33, Philips) at each NIRS probe site. In 2D mode, an average of three manually selected distances was measured from the epidermis to the superficial aponeurosis using a L11-3 linear array transducer. A NIRS

source-detector separation of 30 mm was used allowing for a sufficient signal penetration depth (~15 mm), approximately one-half of the source-detector separation distance. Next, a custom-made wooden sandal was attached using Velcro straps to the foot of the leg that the subject was scheduled to receive an intervention (Figure 3). The wooden sandal device was attached to a load cell pulley system at the head of the patient bed by which individual weights could be added to a bucket by the investigators. The custom-made wooden device has been used in several previous studies in our laboratory (Drew et al., 2013; Luck et al., 2017; Muller et al., 2012; Muller et al., 2015). A cushion was placed under the thigh and ankle, slightly elevating the leg to reduce the influence of venous congestion in the limb. Three sticky ECG electrodes were placed on the patient's chest/abdomen in which heart rate (HR) and cardiac rhythm were monitored using a three-lead electrocardiogram (ECG) (Cardiacap/5; GE Healthcare, Waukesha, WI). A brachial artery blood pressure cuff (Philips SureSigns VS3, Andover, MA) was placed on the subject's right arm and measurements were taken in triplicate prior to starting the baseline. A finger blood pressure cuff was placed around the left middle phalanx of the III or IV digit in which beat-to-beat blood pressure was measured continuously using finger plethysmography (Finometer, FMS, Arnhem, The Netherlands). Subjects were briefly coached on the proper exercise cadence along with the metronome sound cue.

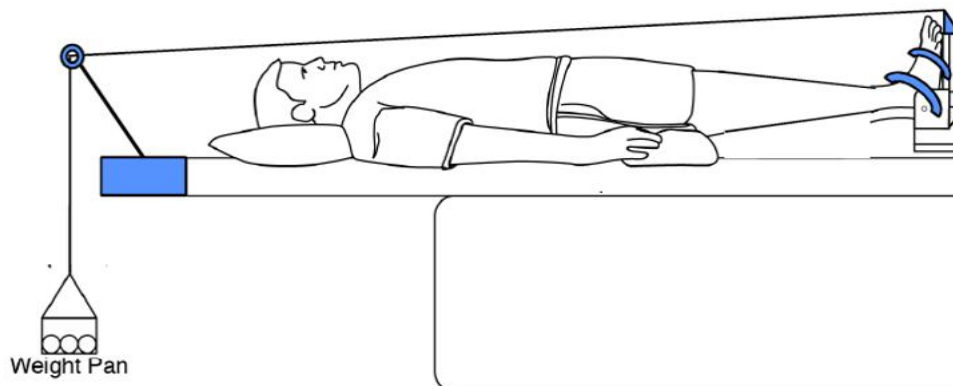


Figure 3. *Experimental setup.* A custom-made wooden sandal with weight and pulley system attached to a patient's foot is shown.

Experimental Visit 1

Following a three-minute baseline, patients underwent supine plantar flexion exercise with the most symptomatic leg starting at 0.5 kg and increasing by 0.5 kg in load every minute until fatigue. Two NIRS monitors were attached to the right and left calf at the region of the medial gastrocnemius. BP and HR were monitored on a beat-by-beat basis during the study. ATT was assessed using ultrasound to ensure the NIRS signal reached the correct tissue depth to penetrate the skeletal muscle.

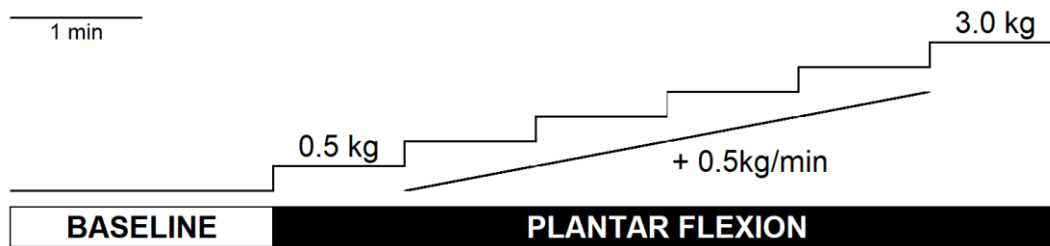


Figure 4. *Exercise protocol.* Following a baseline period, subjects performed supine plantar flexion at 30 contractions per minute with no pause in between contractions for a total of six minutes. A metronome was used to insure proper cadence. Weight was added to a weight bucket at the head of the bed in 0.5 kg/minute increments.

Experimental Visit 2

One month following endovascular or surgical intervention in the lower extremity, patients returned for a second laboratory visit. ABI measurements were repeated and the NIRS monitors were attached in a similar fashion as experimental visit 1 over the right and left medial

gastrocnemius. The measures and exercise protocols were identical to those conducted in visit 1.

Data Collection and Statistical Analysis

Data were collected continuously at 200 Hz and analyzed offline (PowerLab, ADInstruments, Castle Hill, NSW, Australia). NIRS values were collected wirelessly via ANT+ at 2 Hz and transmitted to an offline laptop with ANT+ antenna for offline analysis (PeriPedal v2.4.8; Napoleon, IN). Statistical analyses were performed using IBM SPSS 23.0 software, and graphics were produced using Microsoft Excel. All exercise data were averaged into 20-second bins and the last 20-seconds of each workload were used for statistical analysis. Individual and mean data are presented in changes (Δ) from baseline to 1.5 kg (3 minutes completed) and from baseline to end exercise (i.e., the point at which the subject completed the 3.0 kg, six-minute protocol or stopped prior to completing the protocol due to claudication symptoms). All data were compared with a paired-samples t-test because not every subject completed every stage of the protocol. Data are presented as means (M) \pm standard deviation (SD) and *P* values of <0.05 were considered statistically significant.

Chapter 4

Results

As shown in Table 1, six patients with mild to moderate PAD (2 females and 4 males ranging in ages 55 to 78 years) completed pre- and post-revascularization laboratory visits. Four of the six patients had an improved ABI post-revascularization, while patient 1 improved by only 0.01 and patient 6 decreased from 0.83 to 0.76.

Table 1. *Subject characteristics.*

Patient	Location of Arterial Occlusion	Age (yr)	Height (cm)	Weight (kg)	ABI PRE	ABI POST
1 (F)	Aortoiliac	55	165.1	68.7	0.77	0.78
2 (M)	Femoral-Popliteal	69	182.9	102.5	0.48	0.83
3 (M)	Femoral-Popliteal	67	175.3	118.2	0.79	0.97
4 (F)	Aortoiliac	66	162.6	78.5	0.52	1.01
5 (M)	Aortoiliac and Femoral	78	175.3	85.6	NC	0.52
6 (M)	Bilateral Femoral	63	170.2	83.2	0.83	0.76
M		66	171.9	89.4	0.68	0.81
SD		3	3.1	7.3	0.14	0.07

Individual age, height, weight, and supine ankle-brachial index (ABI) pre- (PRE) and one-month post-intervention (POST) in PAD patients ($n=6$). Data are expressed as means (M) and standard deviation (SD). NC, non-compressible.

Table 2. *Subject comorbidities.*

Comorbidity	Number of patients
Hyperlipidemia	(4/6)
Coronary artery disease	(3/6)
Hypertension	(3/6)
Chronic obstructive pulmonary disease	(1/6)
Peptic ulcer disease	(1/6)

The number of patients with previously diagnosed comorbidities.

Table 3. *The location and number of endovascular or surgical revascularization procedures.*

Type and location	Number of patients
Balloon angioplasty	(4/6)
CIA	(2/6)
SFA	(2/6)
Stent	(4/6)
CIA	(3/6)
EIA	(1/6)
Endarterectomy	(2/6)
CFA	(2/6)
EIA	(1/6)
DFA	(1/6)

After visit 1, all subjects underwent endovascular or surgical revascularization. CIA, common iliac artery; EIA, external iliac artery; CFA, common femoral artery; SFA, superficial femoral artery; DFA deep femoral artery

Table 4. *Pharmacological treatment.*

Medications	Number of patients
Clopidogrel	
PRE	(3/6)
POST	(6/6)
Acetylsalicylic acid	(4/6)
Beta adrenergic receptor blockers	(4/6)
Angiotensin-converting-enzyme inhibitors	(3/6)
Proton pump inhibitors	(2/6)
Bronchodilators	(2/6)
Diuretics	(2/6)
Multivitamins	(2/6)
Antidepressants	(1/6)
Calcium channel blockers	(1/6)
Anti-diabetic medications	(1/6)
Anticonvulsants	(1/6)
Coenzyme Q ₁₀	(1/6)
Vitamin D	(1/6)

After visit 1, all subjects underwent endovascular or surgical revascularization. CIA, common iliac artery; EIA, external iliac artery; CFA, common femoral artery; SFA, superficial femoral artery; DFA deep femoral artery

As shown in Figure 5, changes in muscle oxygenation (SmO_2), assessed with NIRS, are presented for each patient pre- and one-month post revascularization. All six subjects

completed at least the 1.5 kg stage at the pre-revascularization visit while two patients completed the entire 3.0 kg protocol. During the post-revascularization visit, all six subjects completed the 2.5 kg workload with three completing the entire 3.0 kg protocol.

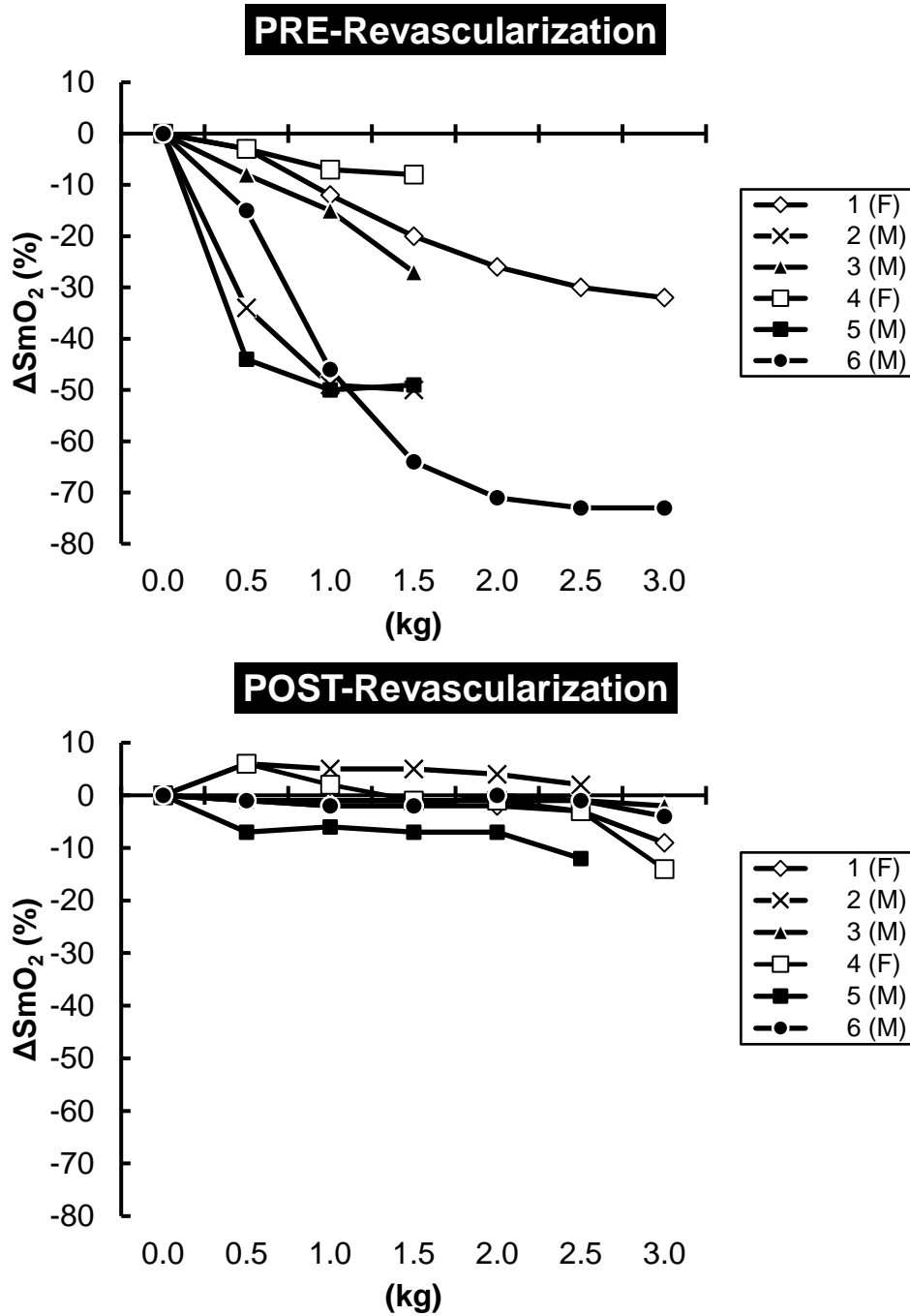
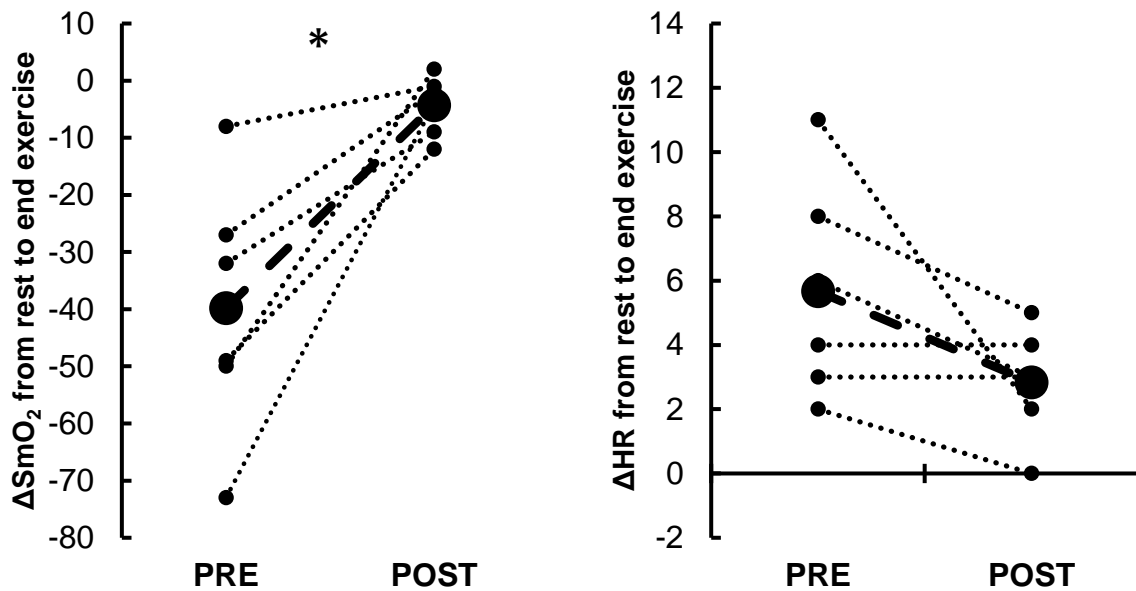


Figure 5. Individual muscle oxygenation responses to plantar flexion exercise in PAD patients ($n=6$) pre- and one-month post-revascularization. Data are collected from the medial gastrocnemius muscle and represent a change (Δ) from rest to end exercise.

The ΔSmO_2 improved post-revascularization at 1.5 kg workload ($-36 \pm 9\%$, PRE vs. $-1 \pm 2\%$ POST, $P < .05$). Similarly, the Δ heart rate was decreased post-revascularization (6 ± 1 bpm, PRE vs. 3 ± 1 bpm, POST, $P < .05$). Exercise intensity that was matched at 1.5 kg did not produce significant findings for blood pressure measurements. When changes were compared from rest to end exercise, as shown in Figure 7, the ΔSmO_2 improved post-revascularization ($-40 \pm 9\%$ PRE vs. $-7 \pm 3\%$ POST, $P < .05$). The end exercise systolic blood pressure was reduced following revascularization (16 ± 6 mmHg PRE vs. 11 ± 4 mmHg POST, $P < .05$) as was mean arterial blood pressure (16 ± 4 mmHg PRE vs. 7 ± 3 mmHg POST, $P < .05$).



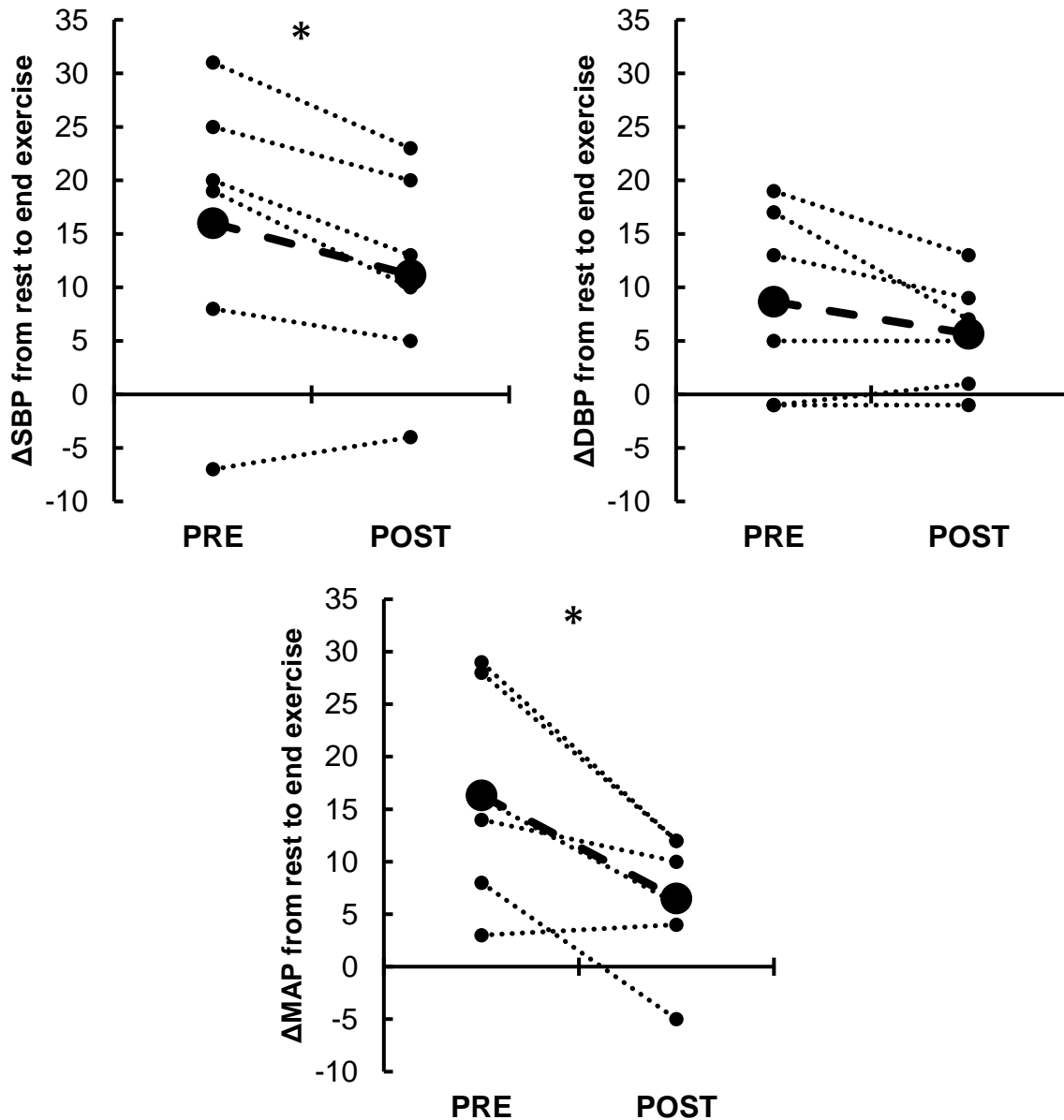


Figure 6. Systemic hemodynamic and muscle oxygenation responses to plantar flexion exercise pre- and one-month post-revascularization. Values represent changes (Δ) from rest to end exercise. Large solid circles and large dashed lines indicate mean values and * indicates significant ($p < 0.05$) difference between pre- and one-month post-revascularization. SmO_2 , skeletal muscle oxygen saturation; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure.

Chapter 5

Discussion

The purpose of this study was to examine whether responses in skeletal muscle oxygen saturation to foot exercise improved one-month post revascularization for the treatment of symptomatic PAD. The novel finding in this study was that oxygenation improved at both 1.5 kg workloads and at fatigue. The blood pressure in PAD patients was improved at end exercise. These results are consistent with previous findings that blood pressure is improved one-month post-revascularization. (Miller et al., 2018). Although the study did not explicitly test for changes in sympathetic nerve traffic, the improvement in muscle oxygenation post-revascularization could have played a role in attenuating the exercise pressor reflex.

Effect of Revascularization on Skeletal Muscle Oxygen Saturation

During exercise, PAD patients have a rapid drop in muscle oxygenation (Bauer et al., 2007; Bauer, Brass, & Hiatt, 2004; Gardner et al., 2019; Luck et al., 2017; McCully et al., 1994; Miller et al., 2017). There does not appear to be a difference in resting oxygenation in PAD. However, initial reductions in oxygenation during exercise are thought to be caused by a widening of the a-v O₂ difference as a result of arterial occlusion. A previous study by Comerota et al hinted that assessing oxygenation before and after revascularization may be important (Comerota, Thom, Kelly, & Jaff, 2003). However, to the best of the author's knowledge, the present study is the first to do so. To date, revascularization appears to be the only thing that rapidly improves oxygenation for up to one month in PAD patients. In one previous study, dietary nitrate supplementation has been shown to improve exercise oxygenation values assessed with NIRS 180 min post-beverage consumption (Kenjale et al., 2011). It is likely that occlusive disease and endothelial dysfunction contributes to these results.

Following revascularization, perfusion to the limb is improved (indicated by an increase in ABI) and may cause the large improvement in saturation during exercise.

Effect of Revascularization on the Exercise Pressor Reflex

Plantar flexion exercise has been shown to elicit a blood pressure raising response called the exercise pressor reflex in patients with PAD (Lorentsen, 1972; Luck et al., 2017; Miller et al., 2018; Muller et al., 2012; Ross et al., 2017). This rise in blood pressure may be caused by sensitization of skeletal muscle nerve fibers that can detect a buildup of metabolic compounds in active tissue. An afferent signal travels to the cardiovascular control centers in the medulla and results in increased sympathetic outflow to the heart and blood vessels of non-active skeletal muscle tissues. Several studies have shown that the exercise pressor reflex is present with a reduction in calf muscle oxygen saturation during exercise (Gardner et al., 2019; Luck et al., 2017; Miller et al., 2017). The present study suggests that by improving large artery blood flow, the exercise pressor reflex is improved at end exercise. While this response was small, it is possible that the post-revascularization blood pressure response could be more pronounced with more vigorous exercise (e.g., during free or treadmill walking).

Limitations

As with many studies in clinical populations, it is difficult to control for covariates (e.g., medications or other treatments) as it would be considered unsafe and/or unethical to interfere with patient care. The PAD patients had different disease locations and received different revascularization treatments for these locations. Although all patients remained on their usual medication regimen, three patients were started on clopidogrel, an anti-platelet medication, following revascularization. It is unclear whether clopidogrel influenced the NIRS

signal in these individuals. However, the other three subjects, who were taking the medication at both visits, showed modest improvements in muscle oxygenation. Apart from these limitations, the results of the study leave several unanswered questions. First, the reduction in muscle oxygen saturation is indicative of either poor tissue perfusion or increased oxygen extraction. However, large artery hemodynamics were not assessed and therefore, it is unclear if the increase in blood pressure during these low intensities was flow restorative. Future studies should investigate femoral blood flow using Doppler ultrasound to understand the changes in responses in large artery hemodynamics to exercise pre- and post-revascularization. To address the issue of extraction versus perfusion at low intensity exercise, utilizing T2*-weighted magnetic resonance imaging could better address this issue. Lastly, it is unclear whether these same results translate to more vigorous exercise tests (e.g., the six-minute walk test or progressive treadmill test (Gardner et al., 1991)). However, as walking function tends to improve in PAD patients post-revascularization (and maybe more so when SET is added to patient treatment (Treat-Jacobson et al., 2019)), any improvements in cardiovascular parameters during exercise could have great clinical significance.

Conclusions

In conclusion, these data suggest the revascularization procedures for the treatment of PAD improve muscle oxygenation and lower blood pressure during dynamic foot exercise. These findings contribute to scientific field in that revascularization treatments, that are intended to improve large artery blood flow, may also have positive benefits on cardiovascular adjustments to dynamic exercise.

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Vita

Jonathan Carter Luck was born in 1990 in Hershey, Pennsylvania, to Dr. Jerry and Kathy Kyper Luck. He received a Bachelor of Science degree in Pre-Professional Biology from Lees-McRae College in May of 2015. In the summer of 2015, He received a Short-Term Research Education Program to Increase Diversity in Health-Related Research Fellowship with the American Physiological Society (R25 HL115473). In the fall of 2015, he began work as a cardiovascular research technologist at Penn State University College of Medicine in Dr. Lawrence Sinoway's laboratory studying exercise responses in patients with peripheral artery disease. During his time at Penn State, He authored and co-authored nine peer-reviewed journal articles that have been published in the *Journal of Applied Physiology*, *Annals of Vascular Surgery*, and *Physiological Reports*. In the fall of 2017, he accepted a research assistantship in Exercise Science at Appalachian State University with Dr. Abigail Stickford and began study toward a Master of Science degree. In the fall of 2018, He earned a 4.0 grade point average and was awarded the North Carolina Tuition Scholarship from Appalachian State University. His Master of Science was awarded in May 2019. In the summer of 2019, he returned to Penn State and continued his research with Dr. Sinoway on a \$9.7 million-dollar National Institutes of Health program project grant (NIH P01 HL134609 and UL1 TR002014 to L. I. Sinoway) to study patients with peripheral artery disease. He continues to guest lecture for several of his former professors, teaching the anatomy and physiology of the cardiovascular system as well as cardiovascular pathophysiology.