THE RETROSPECTIVE REVIEW OF OUTCOMES OF PATIENTS THAT COMPLETED THE VASCULAR REHABILITATION PROGRAM FROM 2020-2023

by

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A THESIS

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Peripheral Artery Disease (PAD) is a chronic and progressive cardiovascular condition that is characterized as occlusion or blockage of arteries that supply blood to the extremities, particularly the legs. A substantial amount of evidence supports exercise as a leading intervention of treating PAD. The search for the most ideal conditions of exercise to have the most significant reduction of PAD has long been explored. **Purpose:** The study aims to retrospectively review the outcomes of the vascular rehabilitation program at PeaceHealth RiverBend. **Methods:** The study conducted included a retrospective review of a preexisting protocol that consisted of multiple parts. The study is designed around many years of research that surround cardiac rehabilitation, however there are many unique aspects to the protocol being described. The protocol being analyzed involves 31 subjects, all of which are enrolled in cardiac rehabilitation through PeaceHealth hospital from 2020-2023. All said patients are known to suffer from PAD. The protocol begins with a warmup on a treadmill at a slow increase in intensity. Once the patient has reached the threshold of which is considered their normal exercise pace, the patient enters the main phase of the protocol. This phase consists of the patients maintaining an exercise pace of which causes a moderate increase in heart rate and blood pressure. **Results:** There was no effect of time($p=0.5561$) on systolic blood pressure, or time($p=0.1931$) on diastolic blood pressure at PRE vs. POST vs. CHANGE. There was a

significant difference on time($p<0.05$) on Metabolic Equivalent of Task (MET) at PRE vs. POST vs. CHANGE. **Conclusion:** The data suggests that the protocol being reviewed had no significant difference on blood pressure but showed significance in increased functional capacity.

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Introduction

Peripheral Artery Disease (PAD) is a chronic and progressive cardiovascular condition that significantly impacts the health and quality of life of millions of individuals worldwide. It arises due to the narrowing or blockage of arteries that supply blood to the extremities, particularly the legs. PAD is predominantly caused by atherosclerosis, a condition characterized by the buildup of fatty deposits (plaques) within the arterial walls, leading to reduced blood flow and oxygen delivery to the affected areas (Kher & Marsh, 2004).This thesis aims to delve into the multifaceted nature of PAD, investigating its etiology, clinical manifestations, diagnostic approaches, and therapeutic interventions. Empirical evidence has repeatedly created an intersection between consistent exercise over time and an improvement in PAD. The scope of the outcomes being reviewed discusses any amount of exercise on a weekly basis. Ranging from 1-3 sessions per week, the research works to question relevant evidence that the protocol used within these sessions serves a beneficial role to improved outcomes in patients with PAD. The protocols in place stem the inquiries: Does an incremental increase in workload on a treadmill reduce the severity of Peripheral Artery Disease? Does an incremental increase in workload on a treadmill allow for an overall decrease in blood pressure? Does treatment of Peripheral Artery Disease improve functional capacity to a significant degree? I hypothesize that as an individual increases their frequency of exercise via the correct protocol, a reduced claudication factor will be observed.

The significance of this research buries its roots in a variety of ways in healthcare and serves to inform on a level beyond the pathology of PAD, taking the form of a multifold project that carries substantial implications in both clinical practice and public health policy.

Investigating current treatment protocols for PAD contributes to a deeper understanding of the effectiveness of these protocols for PAD, specifically within a real-world clinical setting. Examination of the outcomes of the PAD program, helps validate or question the efficacy of the therapeutic approaches used, potentially guiding future treatment modifications if needed (Treat-Jacobson *et al.*, 2019). PAD is often underdiagnosed and may not receive the attention it requires in cardiovascular disease management. Providing data and outcomes on specific interventions aids in the awareness of the importance of chronic cardiovascular disease, thereby enriching the existing literature and emphasizing the importance of addressing PAD with as much urgency as other cardiovascular conditions. Effective management strategies that lead to better patient outcomes can inform health policy, potentially leading to revised guidelines for PAD management. This can also influence funding priorities, encouraging more resources to be allocated toward PAD treatment and research (*Peripheral Artery Disease (PAD) Research | NHLBI, NIH*, n.d.). By potentially demonstrating effective management strategies for PAD, this research could help reduce long-term healthcare costs. Improved management of PAD can decrease the incidence of severe complications, such as limb amputation or severe cardiovascular events, which are costly to treat and manage (Criqui, 2022). Overall, the scope of this research aims not only to contribute valuable data to the scientific community but also has the potential to directly impact patient care practices, healthcare policies, and educational frameworks surrounding PAD.

By examining the real-world effectiveness of PAD management programs, I am hoping to help pave the way for future innovations in treatment and care delivery. Breaking down the complexities surrounding PAD, we can gain valuable insights into its prevention, management, and ultimately enhance patient outcomes. In recent years, the prevalence of PAD has risen

dramatically, primarily due to the increasing incidence of risk factors such as diabetes, obesity, tobacco use, and sedentary lifestyles (Faglia, 2011). Despite its significant impact on public health, PAD often remains underdiagnosed and undertreated, resulting in suboptimal care for affected individuals. Recognizing the urgent need for a comprehensive understanding of this condition, this thesis aims to bridge the knowledge gap and shed light on various aspects of PAD that can guide healthcare professionals, policymakers, and researchers towards more effective strategies for prevention, diagnosis, and management.

The first section of this thesis will explore the pathophysiology of PAD, elucidating the intricate mechanisms underlying the development of atherosclerosis, plaque formation, and subsequent arterial occlusion. By examining the molecular and cellular processes involved, one can identify potential targets for therapeutic interventions and explore innovative approaches to slow disease progression. The second section will focus on the clinical manifestations and diagnostic techniques of PAD. I will explore the diverse symptoms experienced by individuals with PAD, ranging from intermittent claudication (leg pain during exercise) to critical limb ischemia (severe limb-threatening ischemia). Additionally, I will review the various non-invasive and invasive diagnostic modalities available, such as ankle-brachial index (ABI) measurements, Doppler ultrasound, computed tomography angiography (CTA), and magnetic resonance angiography (MRA). The third section will delve into the management strategies for PAD, encompassing lifestyle modifications, pharmacological therapies, and interventional procedures. By examining the evidence-based approaches, one can assess the efficacy of exercise programs, tobacco cessation treatment, antiplatelet agents, lipid-lowering medications, and endovascular or surgical interventions in mitigating symptoms, improving vascular health, and reducing the risk of cardiovascular events. Lastly, this thesis will underscore the importance of a multidisciplinary

and patient-centered approach to PAD care. Recognizing the psychological and socioeconomic impact of this disease allows healthcare providers to integrate comprehensive support systems serving to enhance patient adherence, promote self-management, and optimize long-term outcomes. Through this comprehensive exploration, it is my goal to contribute to the growing body of knowledge on Peripheral Artery Disease and provide healthcare professionals and researchers with valuable insights to improve early detection, appropriate management, and overall care for individuals affected by this prevalent cardiovascular condition.

Existing Literature

Atherosclerosis – Risk Factors

Atherosclerosis is a complex, multifactorial disease characterized by the accumulation of plaque (lipids) within arterial walls, inflammatory cells, and fibrous elements in the large arteries. These factors directly correlate and/or cause the narrowing and stiffening of blood vessels (Li *et al.*, 2020). Several risk factors have been identified as contributors to the development and progression of atherosclerosis, including age, obesity, tobacco use, diabetes, and hypertension (Li *et al.*, 2020). Advanced progression can lead to cardiovascular diseases such as Peripheral Artery Disease, myocardial infarction (heart attack), and cerebrovascular accident (stroke/CVA). The pathophysiology of atherosclerosis involves multiple stages, beginning with endothelial dysfunction. This dysfunction allows the penetration of low-density lipoproteins (LDL) into the arterial wall, where they undergo oxidation. Oxidized LDL is a key proinflammatory factor that triggers the recruitment of monocytes from the bloodstream into the intima of the artery (Bergheanu *et al.*, 2017). These monocytes differentiate into macrophages, which ingest the oxidized LDL, becoming foam cells – a hallmark of early atheroma. As the lesion progresses, smooth muscle cells from the media layer migrate to the intima, proliferate,

and produce extracellular matrix, contributing to the growth and stability of the atherosclerotic plaque. However, under persistent inflammatory stimuli, these plaques can become unstable. The cap covering the atheromatous core may thin and rupture, leading to thrombus formation and acute cardiovascular events (Bergheanu *et al.*, 2017).

While many risk factors for atherosclerosis are modifiable through lifestyle changes, one stands out as unavoidable - aging. As individuals age, cells lose their ability to divide and replicate effectively. Senescence directly contributes to factors such as increased arterial stiffness and reduced elasticity, and more often than not is considered a primary driving factor towards the development of atherosclerotic lesions (Kaneko *et al.*, 2023). Moreover, advanced age often coincides with the presence of other risk factors, further exacerbating the progression of atherosclerosis (Kaneko *et al.*, 2023). Several mechanisms are thought to be behind this increased risk with age, as described in a study published in the Journal of the American Heart Association (JAHA). As briefly mentioned above senescent cells accumulate in tissues, which is causal to the development of pathologies within the Tunica Media and Tunica Intima layers of the endothelium , and can contribute to inflammation and plaque formation (Kaneko *et al.*, 2023). Endothelium, the inner lining of blood vessels, plays a crucial role in regulating blood flow and preventing inflammation. With age, the endothelium becomes dysfunctional, making arteries more susceptible to damage and progressing the plaque formation, leading to fatty arterial buildup. The production of free radicals, molecules that damage cells, increases with age. This oxidative stress can damage blood vessel walls and contribute to atherogenesis (Kaneko *et al.*, 2023). While humans have essentially no control over the ticking clock, focusing on managing modifiable risk factors like diet, exercise, and blood pressure becomes increasingly important as we age to mitigate the increased risk of atherosclerosis.

Obesity is a modifiable risk factor that significantly contributes to atherosclerosis. Obesity negatively impacts the body in several ways. Its impact on the blood vessels makes it one of the leading factors in the development of atherosclerosis and other cardiovascular diseases (Kim *et al.*, 2021). More specifically, obesity functions to hinder homeostasis within the body by disrupting metabolism, progressing insulin resistance, and negatively impacting an individual's lipid profile. Excess fat accumulation, particularly visceral fat around the abdomen, triggers a state of chronic low-grade inflammation throughout the body. This inflammatory environment disrupts insulin signaling, hinders glucose uptake by cells, and promotes the release of free fatty acids into the bloodstream, as well as the dysregulation of adipokines, such as adiponectin (Li *et al.*, 2020). In healthy individuals, these adipokines regulate metabolism, appetite, and insulin sensitivity. However, in obesity, the production of beneficial adipokines like adiponectin decreases, while the production of pro-inflammatory adipokines like leptin and resistin increases (Kim *et al.*, 2021).This hormonal imbalance contributes to the disruption of metabolic processes. Furthermore, inflammatory adipokines blunt the functionality of glucose transporters causing insulin resistance, where the body struggles to utilize insulin effectively, while also preserving the functionality of FoxO1, a transcription factor responsible for the formation of glucose. This process ultimately exacerbates the vessel inflammation and contributes to further plaque formation within the vessel walls by increasing insulin sensitivity (Hardy *et al.*, 2012). Inflammatory processes such as these, promote endothelial dysfunction, meaning that the inner lining of the blood vessels become damaged and inflamed, contributing to loss of function of the semi-permeable membranes of the vessels. Ultimately, this results in impaired blood flow and reduced delivery of oxygen and nutrients to tissues, further compromising metabolic function and recruitment of immune cells (Li *et al.*, 2020). Finally, Obesity is often linked to an unhealthy

blood lipid profile, including elevated triglycerides, elevated LDL cholesterol, and decreased HDL cholesterol. This unhealthy balance accelerates atherosclerosis (Hardy *et al.*, 2012). These disruptions often lead to a vicious cycle: Impaired insulin sensitivity promotes further fat storage, while chronic inflammation and hormonal imbalances continue to disrupt metabolism. This domino effect paves the way for various metabolic diseases. Upon breaking down obesity, it becomes easy to deduce why it serves as a leading factor in atherosclerosis, as well as many other cardiovascular diseases.

Tobacco use is a well-established risk factor for atherosclerosis as well as all other cardiovascular diseases. Tobacco use exposes individuals to numerous harmful chemicals, including nicotine, carbon monoxide, and various carcinogens (Jonason & Bergström, 1987). Smoking-induced oxidative stress triggers endothelial dysfunction, lipid peroxidation, and inflammation, all of which promote atherosclerotic plaque formation. Furthermore, tobacco use decreases levels of protective high-density lipoprotein (HDL) cholesterol and promotes the accumulation of low-density lipoprotein (LDL) cholesterol, exacerbating plaque formation and progression (Hardy *et al.*, 2012). Research provides support for tobacco use having a dose-dependent effect on individuals. As individuals age, studies show a persistent impact of tobacco use into advanced age. Population attributable risk for tobacco use and cardiovascular disease ranges from 14% to 53% according to a cross-sectional study conducted (Murabito *et al.*, 1997). Furthermore, in women who currently smoke, population attributable risk sits at 26% (Murabito *et al.*, 1997). Smokers show a reportable decrease in the effectiveness of antiplatelet medications, resulting in a higher risk of fatality in the event of a cardiovascular event (Murabito *et al.*, 1997). Tobacco cessation, the discontinuation of tobacco products, has shown major improvements in the incidence of intermittent claudication (IC) (Jonason & Bergström, 1987). Intermittent

claudication is the symptomatic expression of lower extremity atherosclerotic disease caused by atherosclerosis in the lower extremities, resulting in a lack of oxygen to the lower extremities of the body (Murabito *et al.*, 1997). Several studies report that the IC risk for ex-smokers 1 year after quitting is similar to the risk factors reported for nonsmokers (Jonason & Bergström, 1987). Along with this, a decreased risk of cardiovascular events, decreased rate of surgical intervention, and improved survival outlook were all associated with tobacco cessation (Jonason & Bergström, 1987). A study done used a population of 343 participants with IC. After one year, 11% had quit smoking and 89% had continued the habit. The group that discontinued smoking reported no lower extremity pain while at rest. On the contrary, of the group that continued to smoke, 16% reported some degree of lower extremity pain at rest (Jonason & Bergström, 1987). Further statistical analysis was done throughout this study that showed positive results toward smoking cessation.

Diabetes Mellitus, both type 1 and type 2, significantly contributes to the development and acceleration of atherosclerosis. While both types of diabetes mellitus impact the cardiovascular system, due to type 2 being significantly more prevalent than type 1, as well as being preventable, for the purpose of this study I will be emphasizing type 2, although cardiovascular risk reduction strategies will apply to both. Hyperglycemia, insulin resistance, and dyslipidemia associated with diabetes promote endothelial dysfunction and oxidative stress, leading to the initiation and progression of atherosclerotic lesions (Grundy *et al.*, 1999). Additionally, diabetes alters the metabolism of lipoproteins, causing high glucose levels in diabetic patients to enhance the oxidation of low-density lipoprotein (LDL) particles, making them more atherogenic. Oxidized LDL is readily taken up by macrophages, forming foam cells that contribute to plaque formation within arterial walls (Kher & Marsh, 2004). Earlier on,

endothelial function was discussed. Diabetes works in tandem with other risk factors by causing Chronic hyperglycemia, impairing endothelial function by reducing nitric oxide availability and increasing the production of reactive oxygen species (free radicals). This dysfunction promotes vascular inflammation, a key factor in the initiation and progression of atherosclerosis (Grundy *et al.*, 1999). Similar to obesity and tobacco use, diabetes alters immune responses and stimulates the release of inflammatory cytokines, leading to systemic inflammation that results in further progression of atherosclerotic lesions (Goldberg, 2004). Diabetes leads to high risk for all cardiovascular disease. A diabetic individual can experience increased platelet reactivity, which heightens the risk of thrombus formation on ruptured plaques, a direct precipitant of acute myocardial infarction and other ischemic events (Goldberg, 2004).

Hypertension, characterized by elevated blood pressure, is a major risk factor for atherosclerosis. The chronic hemodynamic stress associated with hypertension causes mechanical injury to the arterial wall, leading to endothelial dysfunction and impaired nitric oxide production. This process promotes vasoconstriction, inflammation, and oxidative stress, which contribute to atherosclerotic plaque formation (Poznyak *et al.*, 2022). Hypertension also accelerates the progression of existing plaques through increased shear stress, promoting plaque rupture and thrombotic events. Over the course of many epidemiological studies, hypertension has consistently shown to be the highest contributing modifiable risk factor to CVDs (Poznyak *et al.*, 2022). A review that analyzed a variety of CVD studies (Poznyak *et al.*, 2022). reported that hypertension accounts for 48% of all strokes, and 18% of all coronary events. Despite this information, approximately only 40% of patients with arterial hypertension are medicated for the pathology (Poznyak *et al.*, 2022). One of the most concerning pieces of evidence supporting the CVD pandemic was provided via a prospective longitudinal analysis of 36-year follow-up data

from the Framingham Study (Kannel, 1996). The results show that from ages 30-65, on average, there is a 20 mm Hg increase in systolic blood pressure and a 10 mm Hg increase in diastolic blood pressure (Kannel, 1996).

Atherosclerosis is a multifaceted and chronic disease characterized by the build-up of plaques within arterial walls, leading to significant cardiovascular complications. This disease is driven by a complex interplay of modifiable and non-modifiable risk factors. Age, obesity, tobacco use, diabetes, and hypertension are key contributors to its development and progression. The pathophysiological journey of atherosclerosis begins with endothelial dysfunction, allowing the penetration and oxidation of low-density lipoproteins (LDL). This oxidative process initiates an inflammatory response, culminating in the formation of foam cells and the growth of atherosclerotic plaques. Over time, these plaques may become unstable, leading to thrombus formation and acute cardiovascular events such as myocardial infarction and stroke. Age stands out as an unavoidable risk factor, significantly influencing the incidence and severity of atherosclerosis. The natural aging process leads to increased arterial stiffness, endothelial dysfunction, and enhanced oxidative stress, all of which exacerbate plaque formation and progression. Managing modifiable risk factors becomes increasingly crucial with advancing age to mitigate the heightened risk. Obesity contributes to atherosclerosis by disrupting metabolic homeostasis, promoting chronic inflammation, and impairing insulin sensitivity. These metabolic disturbances accelerate plaque development and compromise vascular function, emphasizing the importance of weight management and metabolic health in preventing cardiovascular diseases. Tobacco use is a well-established risk factor that promotes atherosclerosis through oxidative stress, endothelial damage, and inflammation. Tobacco cessation has proven benefits, significantly reducing the risk of intermittent claudication, cardiovascular events, and improving

overall survival. The dose-dependent effect of tobacco use further emphasizes the critical need for cessation programs. Diabetes, particularly type 2, significantly accelerates atherosclerosis through mechanisms such as hyperglycemia, insulin resistance, and dyslipidemia. The resultant endothelial dysfunction and systemic inflammation highlight the necessity of stringent glycemic control and comprehensive cardiovascular risk management in diabetic patients. Hypertension, by exerting chronic hemodynamic stress on the arterial walls, is a major driver of atherosclerosis. Its role in promoting endothelial dysfunction, vasoconstriction, and plaque instability underscores the importance of effective blood pressure management in preventing cardiovascular events. Despite the high prevalence of hypertension, under-treatment remains a critical issue that needs to be addressed to curb the rising incidence of cardiovascular diseases. Overall, atherosclerosis is a complex disease with a multifactorial etiology. While aging is an unmodifiable risk factor, managing other risk factors such as obesity, tobacco use, diabetes, and hypertension through lifestyle changes and medical interventions is crucial in preventing and slowing the progression of atherosclerosis. A comprehensive approach to cardiovascular health can significantly reduce the burden of this disease and improve patient outcomes.

Peripheral Artery Disease – Signs & Symptoms

Peripheral Artery Disease (PAD), also known as Peripheral Vascular Disease, is a chronic circulatory disorder characterized by the narrowing or blockage of arteries that supply blood to the peripheral tissues, most commonly affecting the lower extremities (*Peripheral Arterial Disease (PAD) | Cdc.Gov*, 2022). It is primarily caused by atherosclerosis, a progressive inflammatory condition in which fatty deposits, more commonly known as plaques, accumulate within the arterial walls, leading to reduced blood flow and compromised oxygen and nutrient delivery to the affected areas. Clinically, the locations of manifestation of PAD is nearly always

in reference to the abdominal aorta, iliac, and lower-extremity arteries leading to stenosis or occlusion (Olin & Sealove, 2010). PAD typically develops due to a combination of genetic predisposition and modifiable risk factors, including age, tobacco use, diabetes, hypertension, obesity, and dyslipidemia. These risk factors contribute to the initiation and progression of atherosclerosis, resulting in the development of PAD. However, other non-atherosclerotic causes, such as arterial inflammation (vasculitis), embolism, thrombosis, or arterial dissection, can also lead to peripheral artery disease. In discussion of how it presents in the lower extremities, patients experience classic claudication, atypical leg pain, or no symptoms at all (asymptomatic) (Olin & Sealove, 2010). According to the American Association for Vascular Surgery, there is evidence in support of 50% of patients presenting with asymptomatic disease (Hirsch *et al.*, 2006). In this particular study, a sample size of 460 patients was noted, of which 19.8% has no leg pain upon exertion, 28.5% had atypical leg pain, 32.6% has classic intermittent claudication, and 19.1% had pain at rest (Hirsch *et al.*, 2006).

Intermittent claudication is one of the hallmark symptoms of Peripheral Arterial Disease (PAD), representing a significant indicator of underlying atherosclerotic disease. It is characterized by muscle pain or cramping in the lower limbs, typically triggered by physical activity such as walking and relieved by a short period of rest. The pain results from inadequate blood flow to the muscles due to narrowed or blocked arteries (Ferreira & Macedo, 2010). As mentioned previously, in PAD, atherosclerotic plaques build up within the arterial walls, leading to the narrowing (stenosis) or blockage of the arteries supplying blood to the limbs (Olin & Sealove, 2010). During physical activity, oxygen demand of the muscles increases to keep the muscles functioning at the desired performance. However, due to the stenosed arteries, the blood supply is insufficient to meet this increased demand, resulting in ischemia (Hirsch *et al.*, 2006).

The ischemic muscles generate metabolites like lactic acid, which stimulate nociceptors, causing the characteristic cramping or pain associated with intermittent claudication. Individuals with intermittent claudication typically describe the pain as a cramping, aching, or burning sensation in the calves, thighs, or buttocks. At the onset of claudication, the pain is often mild, increasing with the continuation of exertion. Upon ceasing exertion, the pain dissipates, usually in a prompt manner (Murabito *et al.*, 1997). The symptom pattern is highly reproducible and serves as a reliable clinical indicator of PAD. Intermittent claudication significantly impacts the quality of life. Patients may experience limitations in their physical activities, leading to reduced mobility and independence. The fear of pain can lead to a sedentary lifestyle, which further exacerbates the risk of cardiovascular events and worsens overall health (Olin & Sealove, 2010).

Peripheral Arterial Disease (PAD) is commonly associated with intermittent claudication, but a significant number of patients experience atypical leg pain. Unlike classic claudication, which is characterized by pain in the calf muscles during exercise that subsides with rest, atypical leg pain can manifest in various ways and is often more challenging to diagnose and manage (Gardner *et al.*, 2007). Patients with atypical leg pain may report discomfort in locations other than the calf, such as the thigh, buttock, or foot. The pain experienced may not have a clear correlation with physical activity and can occur at rest. Unlike the predictable onset and relief of pain seen in intermittent claudication, atypical leg pain can have an inconsistent pattern, making it harder for patients to link the pain to specific activities or triggers (Porras *et al.*, 2022). Atypical leg pain can sometimes be confused with other conditions such as arthritis, neuropathy, or spinal stenosis, leading to misdiagnosis or delayed diagnosis of PAD (McGrae McDermott *et al.*, 1999).

Diagnosing & Treating Peripheral Artery Disease

The non-specific nature of atypical leg pain necessitates thorough clinical evaluation and diagnostic testing to distinguish PAD from other potential causes. Tools such as the ankle-brachial index (ABI), Doppler ultrasound, and advanced imaging techniques like computed tomography angiography (CTA) and magnetic resonance angiography (MRA) are crucial in confirming the diagnosis (Olin & Sealove, 2010). Patients with atypical leg pain often experience significant limitations in their daily activities due to the unpredictable and persistent nature of their symptoms. This can lead to a decrease in mobility and overall quality of life. One reputable study done comparing depressive symptoms in different sexes showed results indicating that patients with atypical leg pain are more likely to experience anxiety, depression, and anhedonia compared to those with classic claudication (Jelani *et al.*, 2020). The chronic nature of their symptoms can exacerbate these psychological conditions, further complicating their clinical management.

While many individuals with PAD exhibit symptoms such as intermittent claudication, a significant proportion remain asymptomatic. This asymptomatic presentation of PAD poses unique challenges in diagnosis and management, given the silent progression of the disease and its potential for severe complications (McDermott *et al.*, 2000). Studies indicate that a substantial number of PAD cases are asymptomatic. For instance, a study done in Europe reported that approximately 50% of individuals with PAD do not exhibit typical symptoms such as claudication (Dhaliwal & Mukherjee, 2011). A very similar study also highlighted a significant prevalence of asymptomatic PAD among the general population, with increased risks of cardiovascular events like angina and myocardial infarction in these individuals (Fowkes *et al.*, 1991). Asymptomatic PAD often goes undetected, allowing the disease to progress silently. This

can lead to advanced arterial blockages before any symptoms become apparent, increasing the risk of severe complications such as critical limb ischemia and cardiovascular events. The lack of symptoms in asymptomatic PAD patients can lead to an underestimation of their cardiovascular risk. These individuals may not receive the necessary preventive care and interventions to manage their condition effectively (McDermott *et al.*, 2000). Asymptomatic PAD is independently associated with impaired lower extremity functioning. This underscores the importance of considering functional assessments in asymptomatic individuals to identify those at risk for mobility issues and related complications (McDermott *et al.*, 2000).

Accurate diagnosis of intermittent claudication and underlying PAD involves several non-invasive techniques. The Ankle-Brachial Index (ABI) test is a non-invasive diagnostic tool used to assess peripheral artery disease (PAD). It measures the ratio of blood pressure at the ankle to blood pressure in the arm, providing an indication of peripheral arterial circulation and identifying potential blockages or narrowing of the arteries in the lower extremities. The ABI test is a simple and cost-effective screening tool widely used in clinical practice (Espinola-Klein *et al.*, 2008). An ABI value of less than 0.90 is diagnostic of PAD. This simple, non-invasive test is highly effective in confirming the presence of arterial insufficiency (Espinola-Klein *et al.*, 2008).

Doppler ultrasound is a non-invasive imaging technique that uses high-frequency sound waves to assess blood flow in the arteries. This method is widely used to detect blockages and assess the severity of arterial stenosis in PAD patients (Hiatt *et al.*, 1990). The Doppler probe emits sound waves that bounce off red blood cells moving within the arteries. The returning sound waves are analyzed to determine the speed and direction of blood flow (Hiatt *et al.*, 1990).

Doppler ultrasound is safe, painless, and provides real-time information about blood flow and vessel patency. It can detect even small changes in blood flow and identify areas of reduced perfusion.

Doppler ultrasound is an effective tool for diagnosing PAD in both symptomatic and asymptomatic individuals. It is particularly useful in diabetic patients, who are at higher risk for PAD (Hiatt *et al.*, 1990). Exercise testing is used to evaluate the functional impact of PAD on blood flow during physical activity. This method helps to quantify the severity of symptoms such as intermittent claudication and assess the efficacy of therapeutic interventions. Patients are asked to walk on a treadmill at a set speed and incline. The test continues until the patient experiences claudication pain or reaches a maximum exercise duration (Espinola-Klein *et al.*, 2008). ABI measurements are taken before and after exercise to assess changes in blood flow. A significant drop in ABI after exercise indicates the presence of PAD (Treat-Jacobson *et al.*, 2019). Exercise testing provides valuable information about the functional limitations caused by PAD and helps guide treatment decisions.

Advanced imaging techniques such as Computed Tomography Angiography (CTA) and Magnetic Resonance Angiography (MRA) provide detailed visualization of the arterial system. These methods are used to confirm the diagnosis of PAD, plan interventions, and monitor disease progression (Hiatt *et al.*, 1990). CTA uses X-rays and a contrast dye injected into the bloodstream to produce detailed images of the blood vessels. It can visualize the entire vascular tree, from large arteries to small peripheral branches. CTA is particularly useful for identifying the location and extent of arterial blockages. It provides high-resolution images that help in planning surgical or endovascular interventions (Hiatt *et al.*, 1990).

MRA uses magnetic fields and radio waves to produce images of the blood vessels. A contrast dye may be used to enhance image clarity. MRA is a non-invasive alternative to CTA, especially beneficial for patients with allergies to iodinated contrast dyes or those with impaired kidney function. It provides detailed images of blood flow and vascular structures, aiding in the diagnosis and management of PAD (Hiatt *et al.*, 1990).

Peripheral Arterial Disease (PAD) is a complex and multifaceted vascular disorder primarily driven by atherosclerosis, leading to significant morbidity and mortality. The disease manifests in various forms, from intermittent claudication to atypical leg pain and even asymptomatic presentations, each posing unique diagnostic and therapeutic challenges. The high prevalence of asymptomatic PAD emphasizes the importance of routine screening and early intervention to prevent severe complications. Accurate diagnosis is pivotal for effective management of PAD. Non-invasive techniques such as the Ankle-Brachial Index (ABI) and Doppler ultrasound are essential for initial assessment, offering a cost-effective and accessible means to detect arterial insufficiencies. Exercise testing further aids in quantifying the functional impact of the disease, guiding therapeutic decisions based on the severity of symptoms. Advanced imaging modalities, including Computed Tomography Angiography (CTA) and Magnetic Resonance Angiography (MRA), provide comprehensive visualization of the vascular system, crucial for planning interventions and monitoring disease progression. These techniques offer high-resolution images that are indispensable for identifying the precise location and extent of arterial blockages, thus informing surgical and endovascular strategies. Collectively, these diagnostic methods facilitate a thorough evaluation of PAD, enabling tailored treatment approaches that improve patient outcomes. Continued advancements in diagnostic technology and a deeper understanding of the disease's pathophysiology are essential to enhance the

management and prognosis of individuals affected by PAD. By integrating clinical assessments with advanced imaging, healthcare providers can ensure comprehensive care for patients, mitigating the impact of this pervasive vascular condition.

Relations between atherosclerosis and Peripheral Artery Disease

Atherosclerosis and peripheral artery disease (PAD) are closely interconnected. Atherosclerosis is the underlying pathology that leads to the development of PAD. Atherosclerosis is a chronic inflammatory condition characterized by the accumulation of plaque within the arterial walls, resulting in the narrowing and hardening of the arteries. It is the primary cause of PAD, particularly in the lower extremities. The process of atherosclerosis begins with damage or injury to the endothelial lining of the arteries. This can occur due to various risk factors such as tobacco use, hypertension, hyperlipidemia, and diabetes amongst others. Once the endothelium is damaged, it becomes susceptible to the deposition of lipids, primarily low-density lipoprotein cholesterol (LDL-C), within the arterial wall. The deposition of LDL-C triggers an inflammatory response in the arterial wall. Immune cells, such as macrophages and T cells, migrate to the site of injury and engulf the accumulated lipids, forming foam cells. These foam cells release inflammatory molecules, such as cytokines and growth factors, promoting further inflammation and attracting additional immune cells (Kher & Marsh, 2004).

Over time, the accumulated lipids, inflammatory cells, and cellular debris form a plaque within the arterial wall. The plaque consists of a fatty core (composed of lipids, including cholesterol) covered by a fibrous cap (composed of smooth muscle cells, collagen, and extracellular matrix). As the plaque grows, it narrows the arterial lumen, reducing blood flow to the affected region (Kher & Marsh, 2004).

In the case of PAD, atherosclerosis affects the arteries supplying the lower extremities. The narrowing of these arteries compromises blood flow to the legs and feet. Reduced blood supply means inadequate oxygen and nutrient delivery to the muscles and tissues in the lower limbs, leading to symptoms such as intermittent claudication (leg pain or cramping during physical activity), rest pain, non-healing wounds, and limb ischemia.

The severity of PAD is determined by the degree of arterial occlusion caused by atherosclerosis. Severe occlusions may lead to critical limb ischemia, where the blood flow is severely restricted, increasing the risk of tissue necrosis, gangrene, and limb loss(*Peripheral Arterial Disease (PAD) | Cdc.Gov*, 2022).

It's important to note that atherosclerosis is not limited to the peripheral arteries. It can affect arteries throughout the body, including those supplying the heart (coronary arteries) and the brain (carotid arteries), leading to coronary artery disease and cerebrovascular disease, respectively. The presence of atherosclerosis in one vascular bed often indicates a higher likelihood of its presence in other vascular beds, underscoring the systemic nature of the disease.

Exercise plays a very crucial role in the improvement of PAD. Performing repeated bouts of exercise as an individual experiencing PAD significantly improves symptoms from a multifaceted standpoint. Regular exercise is considered a cornerstone of PAD management and can significantly improve symptoms, functional capacity, and quality of life for individuals with the condition (Crowther *et al.*, 2008).

Regular exercise stimulates the development of collateral blood vessels, which are small, secondary vessels that can bypass narrowed or blocked arteries. These collaterals help improve blood flow to the affected muscles and tissues, reducing symptoms such as intermittent claudication (leg pain or cramping during physical activity) (Crowther *et al.*, 2008).

Exercise has a positive effect on endothelial function, which refers to the health and function of the inner lining of blood vessels. Endothelial dysfunction is commonly seen in individuals with PAD and contributes to impaired vasodilation, increased inflammation, and the progression of atherosclerosis. Exercise promotes the release of nitric oxide, a vasodilator, improving endothelial function and enhancing blood flow to the limbs (Crowther *et al.*, 2008).

Regular exercise helps improve overall fitness levels, including cardiovascular endurance and muscular strength. This increased fitness can lead to improved exercise tolerance and reduced symptoms during physical activity. Individuals with PAD who engage in structured exercise programs often experience increased walking distance before the onset of claudication pain (Crowther *et al.*, 2008).

Exercise, combined with a healthy diet, is instrumental in maintaining a healthy body weight or achieving weight loss. Obesity is a significant risk factor for PAD and can exacerbate symptoms. By reducing body weight, exercise helps alleviate the burden on the lower extremities, making physical activity more manageable and improving symptoms (Faglia, 2011).

Regular exercise contributes to the reduction of blood pressure and improves lipid profiles, such as lowering total cholesterol and triglycerides while increasing high-density lipoprotein (HDL) cholesterol levels. These improvements in blood pressure and lipid levels have a positive impact on cardiovascular health and can slow the progression of atherosclerosis.

PAD is associated with increased systemic inflammation, contributing to the progression of atherosclerosis and the development of cardiovascular complications. Exercise has anti-inflammatory effects, reducing levels of inflammatory markers and promoting a healthier inflammatory profile. This can help mitigate the inflammatory processes involved in atherosclerosis and PAD (Li *et al.*, 2020).

Exercise has been shown to stimulate angiogenesis, the formation of new blood vessels, in individuals with peripheral artery disease (PAD). Angiogenesis is a crucial process that helps improve blood flow and oxygen delivery to tissues affected by PAD (Inampudi *et al.*, 2018). During exercise, the increased blood flow and mechanical forces exerted on blood vessel walls lead to an elevation in shear stress. Shear stress acts as a signaling mechanism that triggers the release of growth factors, such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and angiopoietins, promoting angiogenesis (Inampudi *et al.*, 2018). These growth factors stimulate the proliferation and migration of endothelial cells, which are the building blocks of new blood vessels. Exercise can lead to localized tissue hypoxia, especially in areas affected by arterial narrowing or blockages. Hypoxia-inducible factors (HIFs) are transcription factors that are activated in response to low oxygen levels. HIFs play a vital role in the adaptive response to hypoxia, including the promotion of angiogenesis (Inampudi *et al.*, 2018). Exercise-induced hypoxia can stimulate the activation of HIFs, leading to the release of growth factors and the initiation of angiogenesis. Exercise promotes the production and release of nitric oxide (NO) in the body. NO is a potent vasodilator and plays a role in angiogenesis (Inampudi *et al.*, 2018). NO can enhance the migration and proliferation of endothelial cells, promoting the formation of new blood vessels. Additionally, NO helps improve endothelial function, which is critical for angiogenesis to occur. Exercise induces the release of various pro-angiogenic factors from different sources, including skeletal muscle, adipose tissue, and circulating cells. For instance, skeletal muscle produces myokines, such as interleukin-6 (IL-6) and insulin-like growth factor-1 (IGF-1), which have angiogenic properties (Inampudi *et al.*, 2018). Adipose tissue releases adipokines, such as adiponectin and leptin, which can promote angiogenesis. Circulating cells, such as endothelial progenitor cells (EPCs) and circulating angiogenic cells (CACs), can be

mobilized by exercise and contribute to angiogenesis by integrating into growing blood vessels. Regular exercise has been shown to reduce oxidative stress and chronic inflammation, both of which can impair angiogenesis. By reducing oxidative stress and inflammation, exercise creates a more favorable environment for angiogenesis to occur and promotes the growth of new blood vessels (Inampudi *et al.*, 2018). When engaging in exercise for PAD, it is crucial to follow a structured program that considers individual capabilities, preferences, and medical guidance. Supervised exercise programs, such as the protocol used for this study, have shown significant benefits for individuals with PAD (Crowther *et al.*, 2008).

Methods

IRB Approval

This study was approved by the Institutional Review Board of PeaceHealth (Project #2136546-1) 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. Consent from each patient was not needed due to the review board ruling that this project posed minimal risk to the confidentiality of the patients. Therefore, the project was approved as exempt from needing informed consent.

Subject Characteristics

Thirty one patients were enrolled in the vascular rehabilitation program from 2020-2023 with symptomatic PAD and intermittent claudication were included within this study. Due to this study taking the form of a review, the requirements for study enrollment matched the requirements to be enrolled into the vascular rehabilitation program at PeaceHealth RiverBend.

According to the previous criteria, inclusion criteria consisted of an ankle-brachial index below 0.90 or a toe-ankle index under 0.80, age range from 50 to 80 years, body mass index less than 40 kg/m², and absence of severe walking impairments. Exclusion criteria encompassed uncontrolled diabetes, unhealed diabetic skin ulcers, unstable angina, and recent myocardial infarction.

Study Protocol

The study conducted included a retrospective review of a preexisting protocol that consisted of multiple parts. The study is designed around many years of research that surround cardiac rehabilitation, however there are many unique aspects to the protocol being described. The protocol being analyzed involves 31 subjects, all of which are enrolled in cardiac rehabilitation through PeaceHealth hospital from 2020-2023. All said patients are known to suffer from PAD. The protocol begins with a warmup on a treadmill at a slow increase in intensity. Once the patient has reached the threshold of which is considered their normal exercise pace, the patient enters the main phase of the protocol. This phase consists of the patients maintaining an exercise pace of which causes a moderate increase in heart rate and blood pressure. This intensity is typically maintained for around 2-3 minutes after the onset of claudication. The patient will then rest until the claudication has ceased. Following this the patient will repeat this process 2-3 times. In the final phase of the protocol, the patient enters a cooldown phase. This consists of the patient reaching the point of claudication and then decreasing the intensity of exercise incrementally before stopping. Patients will typically attend this session one, two, or three times per week over a 12 week period. The session is recorded by the attending exercise specialist by measuring the metabolic equivalent of the task, blood pressure, onset of claudication, oxygen saturation, and the total time the patient exercised. This

study will analyze recorded aspects of the protocol in search of significant results. This analysis will aid in determining improvement of PAD symptoms by looking at the initial visits, and final visits, searching for a general trend in improvement of the factors listed above.

Results

Parameter	PRE	POST	CHANGE	P value
Systolic Blood Pressure	134±16	131±21	-3±24	*0.5561*
Diastolic Blood Pressure	74±10	71±11	-3±12	*0.1931*
Metabolic Equivalent of Task	2.2±0.6	3.1±1.1	0.90±0.8	*<0.05*

Table 1. Cardiovascular parameters.

Systolic Blood Pressure, Diastolic Blood Pressure, and Metabolic Equivalent of Task (MET) for subjects across the PeaceHealth RiverBend protocol (Pre vs. Post). Values are reported at mean ± standard deviation. The data were analyzed with a paired two tailed T-Test. *: different from PRE within the group ($p < 0.05$).

Parameter	PRE	POST	CHANGE	P value
Metabolic Equivalent of Task	2.8±0.9	3.6±1.6	0.80±1.1	*<0.05*

Table 2. Metabolic Equivalent of Task for cardiac rehabilitation patients.

Metabolic Equivalent of Task (MET) for subjects across the PeaceHealth RiverBend cardiovascular rehabilitation program (3rd session vs. Post). Values are reported at mean ± standard deviation. The data were analyzed with a paired two tailed T-Test. *: different from PRE within the group ($p < 0.05$).

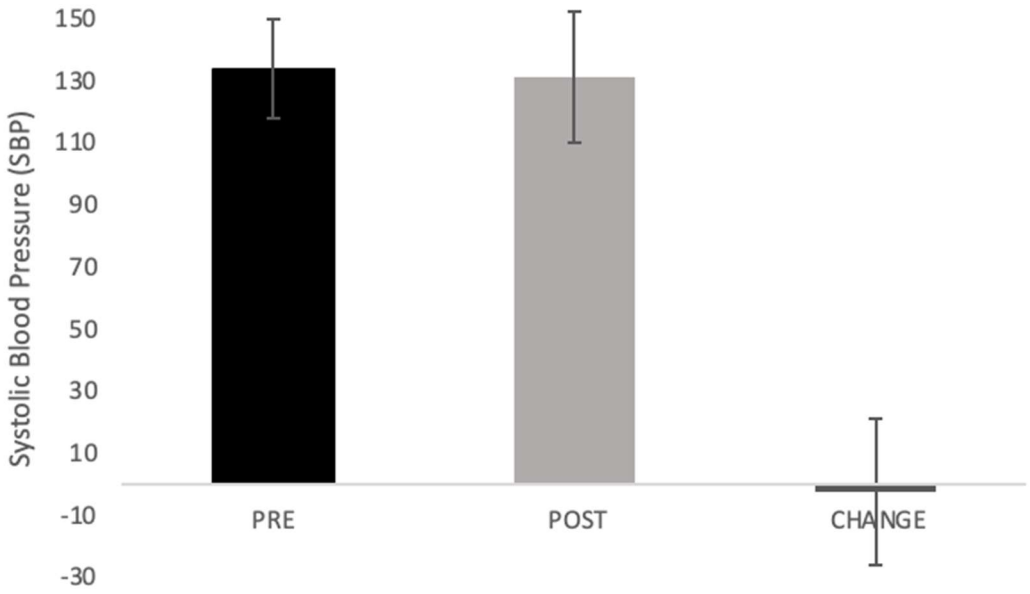

Figure 1. Systolic Blood Pressure.

Average systolic blood pressure across time (PRE, POST, Change) between patients (n=31). Values are reported as mean ± standard deviation. The data were analyzed using a paired two tailed T-Test. *: different from PRE within the group ($p < 0.05$).

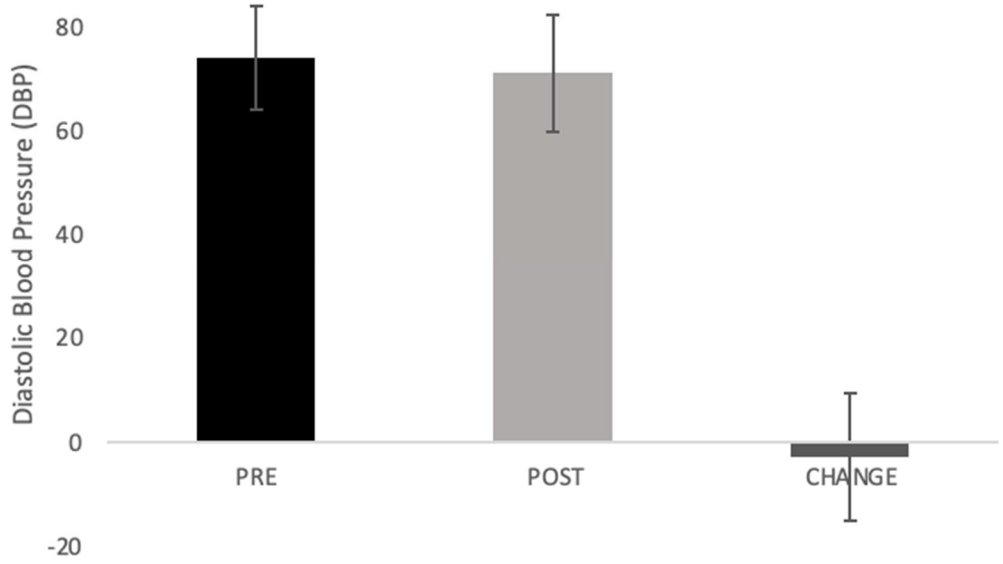

Figure 2. Diastolic Blood Pressure.

Average diastolic blood pressure across time (PRE, POST, Change) between patients (n=31). Values are reported as mean ± standard deviation. The data were analyzed using a paired two tailed T-Test. *: different from PRE within the group ($p < 0.05$).

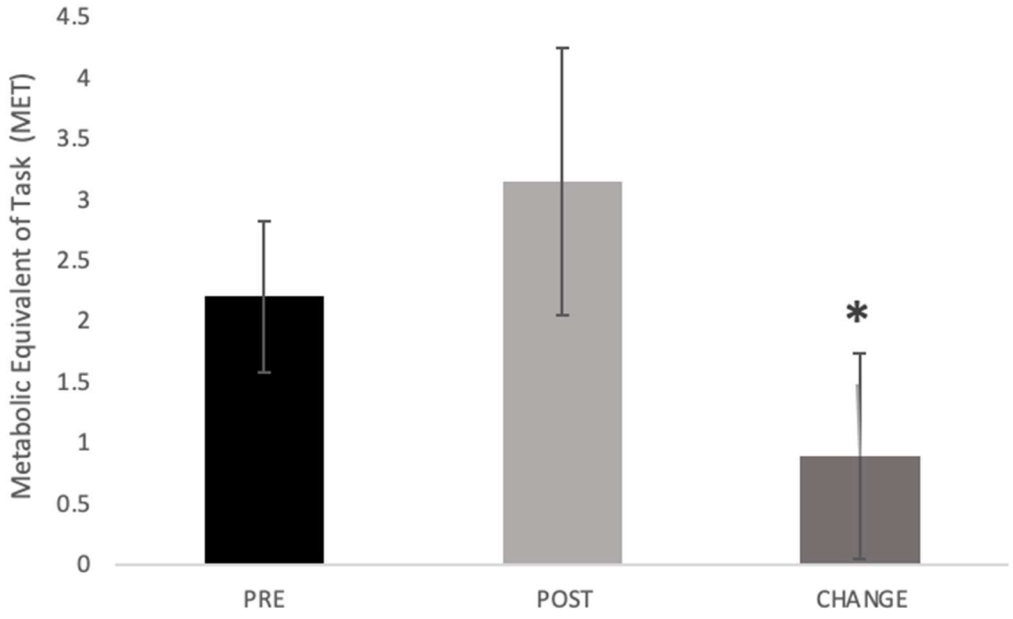

Figure 3. Metabolic Equivalent of Task.

Average Metabolic Equivalent of Task (PRE, POST, Change) between patients (n=31). Values are reported as mean ± standard deviation. The data were analyzed using a paired two tailed T-Test. *: different from PRE within the group ($p < 0.05$).

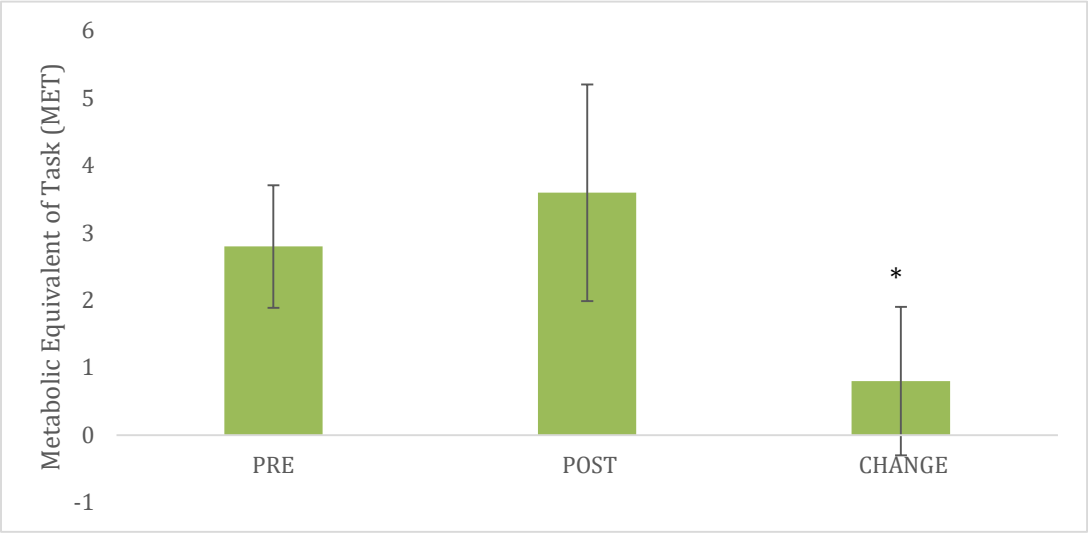

Figure 4. Metabolic Equivalent of Task.

Average Metabolic Equivalent of Task (PRE, POST, Change) between patients (n=332). Values are reported as mean ± standard deviation. The data were analyzed using a paired two tailed T-Test. *: different from PRE within the group ($p < 0.05$).

The data presented in Table 1 and Figures 1, 2, and 3 are a collection of Cardiovascular parameters with 31 patients (n=31). The average number of sessions completed by each patient is 26±9. All 31 rehabilitation sessions were completed across a range from 6 to 36 sessions. Due to these being conducted in a clinical setting, there is no minimum or maximum number of sessions required of any patient included. There was no effect of time ($p=0.5561$) for systolic blood pressure for PRE vs. POST. There was no effect of time ($p=0.1931$) for diastolic blood pressure for PRE vs. POST. There was a significant difference of time ($p<0.05$) for Metabolic Equivalent of Task for PRE vs. POST.

The data presented in Table 2, and Figure 4 is a collection of Metabolic Equivalent of Task parameters from 332 patients (n=332) that completed cardiovascular rehabilitation. There

was a significant difference of time ($p<0.05$) for Metabolic Equivalent of Task for PRE vs. POST.

Discussion

Individuals with Peripheral Artery Disease are at risk for developing cardiovascular disease, which in part can be due to Atherosclerosis. Specially designed exercise protocols may be an effective means to reduce cardiovascular disease, as evident by a reduction of atherosclerosis, and severity of Peripheral Artery Disease symptoms in this population. Claudication factor is a hallmark symptom of classic symptomatic Peripheral Artery Disease. I tested the hypothesis that as an individual increases their frequency of exercise via the correct protocol, a reduced claudication factor will be observed. The main finding within this review is that up to 12 weeks of designed exercise protocols led to an increase in functional capacity. This indicates that patients saw a reduction in symptoms associated with Peripheral Artery Disease. Therefore, we can conclude that these protocols aided in improvement of modifiable risk factors associated with this pathology.

An important finding regarding functional capacity and the efficiency of exercise protocols found within this review looks at cardiac rehabilitation protocols in comparison to vascular rehabilitation protocols. Upon review of the values provided of cardiac rehabilitation patients there was significance seen in increased functional capacity. As we know, a similar result was reached when reviewing the vascular rehabilitation patient's functional capacity values. Using an unpaired T-Test the protocols were compared with the goal of finding significance for one protocol or the other. The result being that there was no significant difference in the efficiency of either protocol when reviewing functional capacity.

Another significant metric that was studied within this protocol was systolic and diastolic blood pressure. I did not see a significant difference in systolic or diastolic blood pressure. This is indicative of the arterial wall pressure not being relieved throughout the 12-week protocol, and likely continued to contribute to cardiovascular strain. Based off previous findings, it is probable that this can be attributed to factors that cannot be maintained within a patient population. For example, diet, obesity, tobacco use, age, and other risk factors. Had we come up with a method of controlling these variables, our results may have warranted a trend in improving blood pressure.

In relation to all the information provided above, one needs to consider the possible findings and outcomes that could arise from analyzing a 12-week exercise program designed to improve peripheral artery disease (PAD). This type of research can yield several positive findings and improvements in individuals with the condition. One of the primary goals of an exercise program for PAD is to increase the distance individuals can walk outside of a clinical setting without experiencing symptoms such as leg pain or cramping (intermittent claudication) (Crowther *et al.*, 2008). After a 12-week exercise program, individuals may observe an improvement in their walking distance before the onset of symptoms. They may be able to walk for longer durations or cover more ground, indicating increased exercise tolerance and improved peripheral circulation (Crowther *et al.*, 2008). Another possible outcome that could occur relates to the alleviation of the severity of intermittent claudication symptoms. Individuals may experience less pain, discomfort, or cramping during physical activity, allowing them to engage in more prolonged and productive exercise sessions (Crowther *et al.*, 2008). This reduction in symptom severity can enhance quality of life and encourage individuals to maintain an active lifestyle. Finally, the study could report enhanced functional capacity, arguably the most

important improvement. Following a 12-week exercise program, individuals may experience improvements in their overall functional capacity. They may find it easier to climb stairs, walk up inclines, or perform other activities that were previously challenging (Crowther *et al.*, 2008). These improvements reflect the enhanced strength, endurance, and cardiovascular fitness gained through regular exercise.

Conclusion:

Regular physical activity within a structured rehabilitation program enhances endothelial function, reduces systemic vascular resistance, and promotes arterial health, contributing to lower resting blood pressure levels. Additionally, improved blood pressure regulation aids in better exercise tolerance and functional capacity, allowing patients to engage in daily activities with less discomfort and greater mobility. The integration of aerobic and resistance exercises in vascular rehabilitation proves essential in managing PAD, offering significant benefits that extend beyond mere symptom relief to encompass overall cardiovascular risk reduction and enhanced quality of life. Continued research and implementation of tailored exercise programs are vital in optimizing outcomes for individuals undergoing vascular rehabilitation.

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