Improving mobility in peripheral artery disease using an ankle foot orthosis
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1. Specific Aims

Peripheral artery disease (PAD) is a common cardiovascular disease manifesting from atherosclerotic blockages in the arteries of the legs. The most prevalent symptom of PAD is intermittent claudication, defined as pain or discomfort in the legs that is produced by physical activity and is relieved only through rest. PAD results in significant functional limitations such as slower walking velocity and an overall sedentary lifestyle[1-5]. Our research has documented significant deficits in gait biomechanics; specifically, an inability of the ankle plantarflexors to generate normal torque and power[6-10]. Furthermore, we found that insufficient blood flow is not the only mechanism contributing to gait dysfunction in patients with PAD[11, 12], but the affected muscle also demonstrates a myopathy that prevents normal leg function in these patients[13-17]. Thus, treatment must consider muscular function and hemodynamics to improve function and increase activity levels.

Supervised treadmill walking exercise is an effective treatment for increasing the distances patients with PAD can walk [18-21]. However, there is a critical treatment gap for individuals whose disease presentations warrant a non-operative treatment plan but lack the motivation, time, access and monetary resources for supervised therapy. An ankle-foot orthosis (AFO) to offset ankle plantarflexor torque and power deficiency is a novel approach to increase the walking distances and physical activity levels in those with PAD. Made of a carbon-composite material, AFOs are adjustable, affordable and could be prescribed and worn long-term to overcome the reduced propulsion and improve walking economy[22-26]. The spring-like properties of carbon-composite AFOs allow energy storage at weight acceptance and return at the point of toe off, when the ankle plantarflexors are supposed to propel into the next step[27, 28]. Improvements in ankle kinetics and angular momentum have been reported by using an AFO with stroke, and other neuromuscular disorders affecting the legs[22-25]. However, AFOs are typically worn for foot drop, and have never been implemented in patients with PAD to improve forward propulsion. Our pilot work has shown that walking with an AFO instantly increases the initial and absolute walking distances in patients with PAD as much as pharmacotherapy for six months[29]. An AFO addresses both the myopathy and low blood flow problems associated with claudication. Mechanical force from the AFO compensates for the insufficient propulsion force of the myopathic gastrocnemius muscles, while at the same time decreasing blood flow demand and muscular stress effects of ischemia. Thus an AFO allows patients to walk longer without pain or walk the distance needed to complete daily activities with less stress to the affected leg, and may preserve/improve the overall health of the PAD limb by lowering oxygen demands to PAD muscle and effort induced ischemia and stress.

Hypothesis: An AFO improves walking performance in patients with PAD by reducing the energy cost of walking and these improvements can be seen from the first time the patient uses the AFO. Further, an AFO intervention improves walking performance by improving the muscular function of patients' affected legs.

Specific Aim 1: Test the hypothesis that from its first use an AFO produces improvements in walking performance of patients with PAD by decreasing the required muscle contribution and energy cost of walking.

Specific Aim 2: Test the hypothesis that using an AFO for three months leads to progressive improvements in walking performance, physical activity levels and quality of life of patients with PAD and that these improvements correlate with improvements in the morphometric measurements, oxygenation levels, and muscle strength and endurance characteristics of the affected legs. We will use a crossover design, in which half of subjects will complete a three-month control period before, and half after, the AFO intervention.

Specific Aim 3: To determine the feasibility of a three month AFO intervention by examining acceptability (satisfaction, intent to continue use), demand (actual use, perceived demand), implementation (degree of use, success or failure of use, factors affecting use), and practicality (effects, ability of participants to use AFO).

If our hypothesis is correct, will be the first to demonstrate that a simple, accessible AFO device can rapidly improve functional status and quality of life in patients with PAD immediately by decreasing the required muscular contribution and oxygen demands to PAD muscle. Additionally, Aim #2 will evaluate the long-term effects of wearing an AFO on functional status and quality of life. Aim #3 will help the investigative team ensure it is feasible to implement the AFO in our target population. Detailed measures of mechanisms related with walking performance, muscle contribution, physical activity, quality of life and how these mechanisms change after wearing the AFO for three months will provide the evidence required to implement an AFO therapy that will improve functional status and quality of life in individuals with PAD.

2. Significance

Current treatments for PAD do not compensate for muscle myopathy

Lower extremity peripheral artery disease (PAD) is a prevalent atherosclerotic syndrome that produces progressive narrowing and occlusion of the arteries supplying the legs[5]. PAD affects approximately 8 million people in the US, producing a considerable public health burden[30]. Most PAD patients are older adults and in populations older than 70 years the prevalence of PAD increases to 20%[5]. The cardinal manifestation of PAD is claudication, a severe functional limitation identified as gait dysfunction and painful tightness or cramping in the muscles of the leg caused by walking and relieved by rest. The prevalence of claudication is expected to rise due to the anticipated aging of the population and there is a clear and unmet need for effective treatment[31]. The standard therapies for claudication include pharmacotherapy, supervised exercise therapy, endovascular revascularization (angioplasty/stenting) and open revascularization (bypass operations)[9]. The two medications currently approved for the treatment of claudication in the US are pentoxifylline (a methylxanthine derivative) and cilostazol (a phosphodiesterase type 3 inhibitor). Both medications have modest efficacy and a recent systematic review concluded that pentoxifylline and cilostazol are associated with improvement in maximal treadmill walking distance of only 15% and 25%, respectively[32]. Supervised exercise therapy is more effective but unfortunately is associated with poor compliance. Moreover, Medicare and most medical insurance companies do not pay for exercise therapy, limiting access to it. Finally, endovascular and open revascularization offer greater degrees of improvement but are associated with considerable morbidity and poor long term patency[40, 41] **(Table1)**. These treatments all require time to take effect (3-6 months for pharmacotherapy and exercise), or require time for recovery (at least 3 months for endovascular and open revascularization procedures). Furthermore, all available treatments primarily target the blood flow limitation of PAD while very little is done for the ischemic myopathy in the legs of patient with PAD, which has been shown to be a key determinant of decreased walking performance in patients with PAD[42, 43].

Treatment	% Increase In Maximum Walking Distance	Refs
Pentoxifylline	15%	32
Cilostazol	25%	32
Ramipril	123%	33
Supervised exercise	120%	34, 35
Endovascular revascularization	90%	36-38
Open bypass revascularization	172%	39

Table 1. Effects of treatment on absolute walking distance.

Our research has documented significant deficits in gait biomechanics in patients with PAD compared with healthy, aged matched controls. Our studies show that PAD results in inability of the posterior calf muscles, the ankle plantarflexors, to generate normal torque and power by the lower extremity joints[6-10]. We have also shown that in PAD gait dysfunction is not only a result of inadequate blood flow[11, 12], but also the product of an ischemic myopathy affecting the leg muscles of patients with PAD[13-17, 44]. An AFO can immediately provide mechanical compensation for ankle plantarflexor torque and power deficiency through energy storage and return (Figure 1). Made of a carbon-composite material (Figure 2), off the shelf AFOs are adjustable, affordable and could be prescribed to overcome reduced propulsion and improve walking economy[22-26]. The spring-like properties of carbon-composite AFOs allow energy storage at weight acceptance and returns at the point of toe off, when the ankle plantarflexes and power is required to

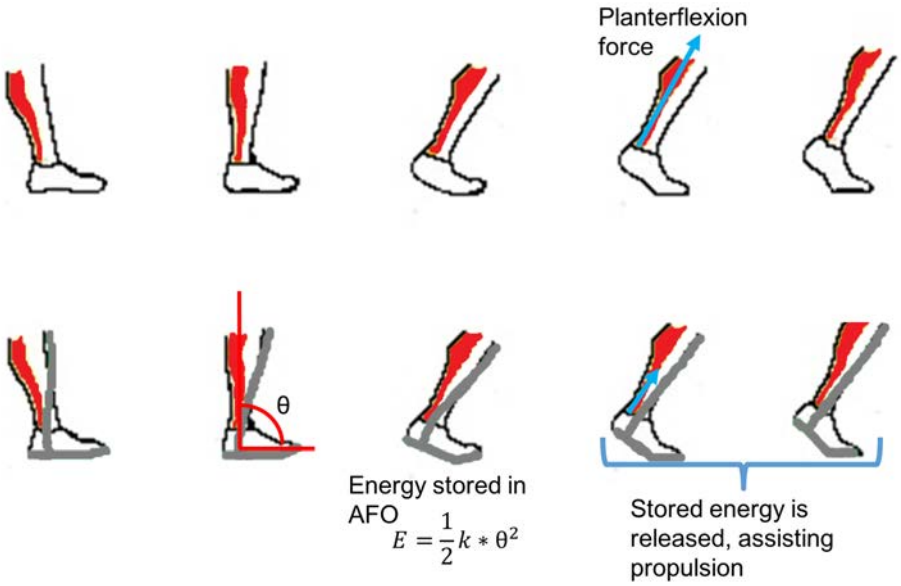

Figure 1. The ankle plantarflexors contribute torque during the propulsion phase at the end of stance. This diagram illustrates required plantarflexor force during normal walking (top) and while walking with an AFO (bottom). The red arrows represent reduced plantarflexor force contribution with the AFO. The AFO contributes to torque at the end of propulsion is shown by bending during weight acceptance, which stores energy in the carbon composite material that is later released during propulsion. The moment generated by the AFO is equal to the AFO stiffness (k) times the change in the AFO angle (θ).

propel the body into the next step. AFO devices have stimulated excitement in regards to their potential for improving walking performance in individuals with movement disability. In individuals with stroke, hemiplegia, and other motor disorders[22-25] that have inadequate lower extremity torque and power during walking, an AFO has been shown to help restore walking performance[26, 28, 45]. The AFO can similarly be used to address this need of a non-operative, efficacious intervention that directly increases the functional status in patients with PAD. The results of such an intervention on muscle performance, physical activity levels, and quality of life present mechanistic research questions that can improve the care of patients with PAD.

Figure 2. Carbon-composite ankle-foot orthosis. The spring-like properties of carbon composite allows energy to be stored during heel strike and returned at the point of toe-off.

Objective of our application and significance of proposed work:

An AFO can directly increase the distance patients with PAD can walk: Patients with PAD are limited in the distance they can walk and also demonstrate increased energy costs of walking compared with healthy aged-matched individuals[46-49]. We will test whether wearing an AFO can instantly improve the functional status of patients with PAD. Walking performance will be assessed using walking distances, and lower extremity torque and power contribution measured by gait biomechanics. Interventions often target blood flow improvements in patients with PAD, but the AFO takes a different approach by addressing both the blood flow limitation and the myopathy of PAD legs. The AFO can reduce ischemia by decreasing the demand for blood flow during walking and can also compensate for myopathy-related muscle weakness by providing propulsion torque at the end of stance. Previous studies in elderly and patients with neuromuscular diseases show that an AFO maintains the overall ankle torque and power profile by allowing a reduction in the contribution needed from ankle plantarflexor muscles. We hypothesize that the use of an AFO will improve the walking distances of patients with PAD by reducing the energetic requirements of the myopathic PAD legs and the energy cost of walking.

Patients wearing an AFO device for three months will progressively improve walking performance and increase physical activity levels. The work of our group and others demonstrates that a state of repetitive cycles of exercise-induced ischemia followed by reperfusion at rest is associated with episodes of claudication and contributes to the muscle degeneration and possibly even the excess morbidity and mortality seen in these patients[15, 17, 50, 51]. It is possible that treating a claudicating patient with an AFO decreases the severity of these ischemia/reperfusion events and results in local protection to the treated leg and its muscles and the body as whole. If this hypothesis is correct then we can expect that treatment with the AFO may improve the muscle histological and biochemical characteristics, muscle strength and performance, walking distances and overall activity levels[21].

Patients with PAD are sedentary compared with their healthy peers, and this sedentary lifestyle is associated with faster declines in functioning and adverse calf muscle changes[52-54]. Thus, the goal of the proposed AFO intervention is to reverse this negative cycle by increasing the ability of patients with PAD to walk. The distance that older individuals can walk is directly correlated with muscle strength and ankle plantarflexor torque generation. Additionally, the mitochondrial function and oxidative capacity of the plantarflexor muscles of older individuals is more affected by physical activity levels than age.[55, 56] Therefore, enabling individuals to walk more could promote increases in muscle strength and endurance, muscle morphometric measurements, and improvements in muscle oxygenation levels, which translate to overall increased walking performance, physical activity levels, and quality of life. The concept that patients with PAD will walk more with the AFO is based on the premise that wearing the AFO will prolong the onset of pain and results in fewer occurrences of claudication pain throughout the day.

Little work has been done to enhance adherence to treatment in PAD

Adherence to treatment is a critical component to the efficacy of any intervention. Without adherence, even an effective intervention has no impact. Thus feasibility measures are warranted when testing the utility of a new intervention technique to assess patients' acceptability (satisfaction, intent to continue use), demand (perceived demand), implementation (degree of use, success/failure of use, factors impacting use), and practicality (positive/negative effects, ability of participants to use) of the treatment. Research in several fields has examined the efficacy of braces and other devices to improve health outcomes. For example, Armstrong

and colleagues (2003)[57] examined diabetic patients' adherence to a pressure off-loading device used to treat foot ulcerations. They found patients had minimal wear time which partially explained the poor results of the study. While the authors speculated on why adherence was low, there was no information on the reasons for low adherence from the patients' perspective. Gathering information from the patients' point of view is necessary to understand whether a new treatment is feasible for patients. Unfortunately little is known about how individuals with PAD adhere to treatment. Assessing the feasibility of a new treatment is crucial to its application in future studies and can determine if additional educational interventions to improve adherence are needed[58]. In individuals with PAD, walking exercise is a good example of an effective treatment that has been difficult to get patients to adopt unless it is supervised. In previous studies of supervised exercise that demonstrated increases in walking distances, non-supervised control groups did not show improvements. [20, 59, 60] There are likely many factors that play a role in non-adherence, including leg symptoms, feelings of decreased mobility, low motivation, and low self-efficacy, ones' belief in his or her capacity to execute the desired behavior change[61]. In studies of exercise adherence in elderly individuals, pain is the top reason for non-adherence. [62] It could be assumed that symptomatic claudication pain is also the top reason in patients with PAD. Research in individuals with PAD has shown that self-efficacy plays a vital role in adherence to exercise. [63, 64] Thus, decreasing the onset of pain through an AFO is likely to help patients address the number one barrier to exercise. The lack of improvement in non-supervised individuals emphasizes the need for developing interventions that will be adapted by the patients. Additional work to determine treatment adherence barriers in individuals with PAD is limited due to lack of additional conservative therapies in this group. Thus, the third specific aim will seek to ensure the AFO device is something that will be adapted by patients. Patient interviews will capture information on the feasibility of the AFO intervention by capturing acceptability, demand, implementation, and practicality. We will use this information to inform modifications to the device itself or ways to implement it in patients with PAD.

Improvements in gait and ankle kinetics have been reported by using an AFO in individuals with neurological disorders and in the elderly. However, an AFO has never been used to help the gait deficiencies of patients with PAD. In this study, we will determine whether wearing a carbon composite AFO leads to a clinically important improvement in walking performance, examine changes in walking performance, physical activity, and quality of life following a three month intervention, and investigate multiple facets of the intervention to improve patient compliance. We propose that these immediate walking performance improvements are the result of reduced energy costs for those wearing the device, as previous studies have demonstrated the device replaces ankle torque and power. [22-25] Further we propose the mechanisms of improved morphometric parameters, muscle oxygenation, and muscle strength and endurance of the affected legs facilitate improvements seen following the intervention.

3. Innovation

The resources of our research group are focused on interventions to improve leg function in patients with PAD and we have developed a history of effective patient recruitment and collection of gait data before and after therapeutic intervention. Consequently, we have a unique capability to study the effects of interventions on walking performance, along with the mechanisms behind those effects. We have actualized this capability by coupling our expertise in biomechanics and behavioral intervention with extensive clinical expertise. The result is a well-rounded team of scientists equipped for evaluating and refining a new intervention that has great potential to impact functional status and quality of life in patients with PAD. Our findings that the ankle plantarflexor muscles are the most consistently and greatly affected muscles, combined with our work demonstrating muscles of these patients fail at the histological and biochemical levels, have directed us to a novel yet simple intervention that can assist these muscles. We see the AFO as a way to address the problems of insufficient blood flow and muscular myopathy to enable performance of normal daily activities.

Most conservative approaches to treatment have involved some form of supervised exercise. While exercise therapy can be effective in improving the distance patients can walk, it does not have an immediate impact. Implementing the simple yet novel intervention of a carbon composite AFO, our study will test the mechanisms contributing to both acute and long-term improvements in walking performance, and provide the evidence required to successfully implement the AFO as a therapy in this population. This project will provide the evidence needed to introduce an easily accessible intervention that can be utilized in the clinical setting. Furthermore, our findings will be used to develop additional rehabilitation studies aimed to improve muscle health and function in PAD.

4. Approach

Preliminary work demonstrates forward propulsion is deficient in individuals with PAD. [6-8, 10, 65]

We have conducted several studies evaluating ground reaction forces (Figure 3), joint angle kinematics, and joint muscular responses (joint torques) and their contributions (joint powers) during the stance phase of gait in patients with PAD.

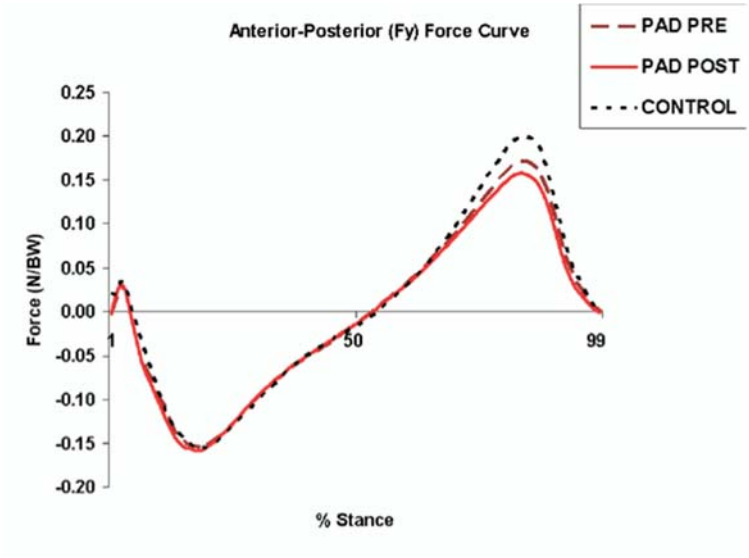

Figure 3. Anterior-posterior (front-to-back) ground reaction force curves for patients with PAD prior to the onset of claudication (PRE) and following the onset of claudication (POST); and healthy controls (CONTROL). Decreased peak propulsion towards the end of the stance phase in the PAD group is consistent with inability of the ankle plantarflexor muscles to generate force to propel individuals into the next step just before the toe comes off the ground. This decrease occurs prior to the onset of pain and worsens slightly during the PAD POST condition.

In the first study, we compared ground reaction forces of 14 patients with PAD (Age: 58 ± 3.4 years; Body Mass: 81.0 ± 15.64 kg) to five healthy controls (Age: 53 ± 3.4 years; Body Mass: 87.4 ± 12.75 kg)[65]. In this study we analyzed ground reaction forces. Additionally, we evaluated stance time and time spent in double-limb support. Results demonstrated that in the anterior-posterior force direction, the propulsion forces used for push-off in late stance were significantly decreased in patients with PAD (Figure 3). Regarding stance time and time spent in double support, patients with PAD had significantly increased values compared with healthy controls. All of these differences were even present during a pain free (rested) state in patients with PAD.

In several follow-up studies in patients with PAD, we evaluated joint muscular responses and their contributions by calculating joint torques and powers of the ankle, knee, and the hip during walking (Figure 4).

The first such study evaluated lower extremity joint torques in 13 patients with PAD who exhibited bilateral intermittent claudication (Age: 64.5 ± 8.57 years; Body Mass: 80.7 ± 12.64 kg) and 11 healthy control subjects (Age: 66.2 ± 9.22; Body Mass: 77.8 ± 10.75 kg). The conditions included walking prior to the onset of claudication pain and walking after the onset of pain[10]. Compared to controls, patients with PAD had significantly decreased hip extensor torque during early stance in both conditions. During the pain condition, patients with PAD had significantly decreased ankle plantarflexor torque during late stance. We conducted a follow-up study in 20 patients bilateral PAD (Age: 60.3 ± 7.21 years; Body Mass: 82.6 ± 18.05 kg) and 16 healthy controls (Age: 62.8 ± 12.01; Body Mass: 81.8 ± 20.99 kg) that evaluated joint torques and also joint powers[7], which was the first study to investigate joint powers in patients with PAD. Patients were assessed while walking before and after the onset of claudication pain. Patients with

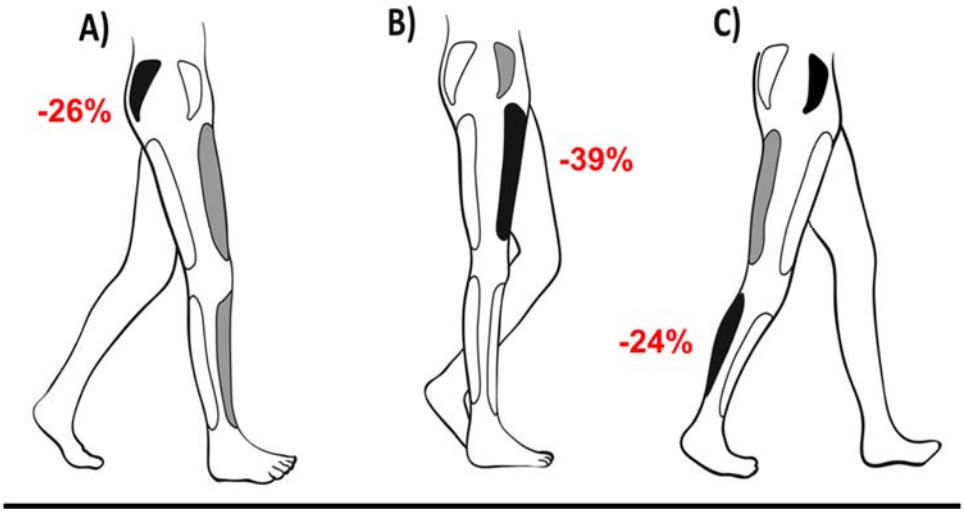

Figure 4. Average decreases in joint power contributions during each phase of stance in patients with PAD compared with healthy controls from previously published studies[6-8, 10]. There are significant average decreases at all three joints during various phases of stance in individuals with PAD. In another group of individuals with decreased ankle torque and power at the end of stance, healthy older, the hip compensates by increasing the hip extensor torque during weight acceptance. As is evident in this figure, individuals with PAD do not compensate in this way.

PAD had significantly decreased hip and knee power during early stance due to decreased torques produced by the hip and knee extensors. Knee and hip power was also significantly decreased during midstance, which is attributed to decreased torques produced by the knee extensors and the hip flexors. During late stance, reduced propulsion was noted by a significant reduction in the ankle plantarflexor torque and power. All of these reductions in patients with PAD were present prior to and after the onset of claudication pain.

We have also performed a similar biomechanical evaluation in 12 unilateral patients with PAD (Age: 61.7 ± 10.53 years; Body Mass: 84.7 ± 20.24 kg and 10 healthy controls (Age: 66.3 ± 9.22; Body Mass: 77.9 ± 10.65 kg)[8]. Results of this study further confirmed the deficiencies of the ankle plantarflexors in propelling the body forward, as ankle plantarflexor torque was significantly reduced in the affected limb as compared with controls before and after the onset of claudication pain. Additionally, ankle plantarflexor power was significantly decreased on both affected and unaffected limbs of patients with PAD as compared to controls. Although ankle torque and power are often reduced in healthy older individuals, older compensate by increasing the hip extensor torque and power[66]. Here, the PAD group experiences deficits at the ankle, knee, and the hip rather than compensating with a different joint like we see in healthy older individuals. In sum, we estimate that average reductions in joint torques during each phase of stance from all of our previous studies are 24% decrease in hip power generation during early stance, 39% decrease in knee power generation during midstance, and 26% reduction in ankle plantarflexor power generation during late stance as compared with healthy controls (Figure 4) [6-8, 10].

Collectively, these studies demonstrate patients with PAD have deficits in the muscular contribution of the ankle plantarflexors, which decrease propulsion during walking. Ankle plantarflexor torque and power in late stance is of great importance as it represents the greatest contribution to overall power during ambulation. The findings from these preliminary studies motivated the intervention to increase propulsion with an AFO.

Supervised exercise therapy improves peak walking distances but not lower extremity torques and powers. Preliminary unpublished data from our laboratory was collected in 23 patients with PAD (Age: 60.3 ± 7.21 years; Body Mass: 82.6 ± 18.05 kg) who completed a supervised walking program for six months. Joint torques and powers were calculated from subjects walking prior to the onset of claudication pain at baseline and after the exercise program. Of the 23 subjects collected, the ankle plantarflexor torques were unchanged or worsened (decreased torque) in 14 subjects following the exercise program (Figure 5). To examine whether patients with PAD were able to redistribute joint torque following the exercise program, we investigated hip extensor torque in early stance. Redistribution of torque is a strategy to use one joint to compensate for a deficit in another joint, to achieve propulsion during walking. However, instead of torque redistribution, we found similar decreases in the hip as the ankle, with 13 of the 23 patients having no change, or further decrease, in peak hip extensor torque following the exercise intervention (Figure 6). Regarding power, a total of 16 patients had unchanged or decreased ankle plantarflexor power (Figure 7), and 11 patients had unchanged or decreased hip extensor power after participating in supervised exercise for six months (Figure 8). Of note, all 23 subjects improved the peak walking distance 685 meters on average. Of subjects whose ankle plantarflexor torque did not improve, their peak walking distances were still increased an average of 669 meters. While it is a positive result that patients are increasing the maximum distance that they can walk after completing a six month exercise program, lack of improvement in gait biomechanics means there is untapped potential for further improvements in the walking performance of these individuals.

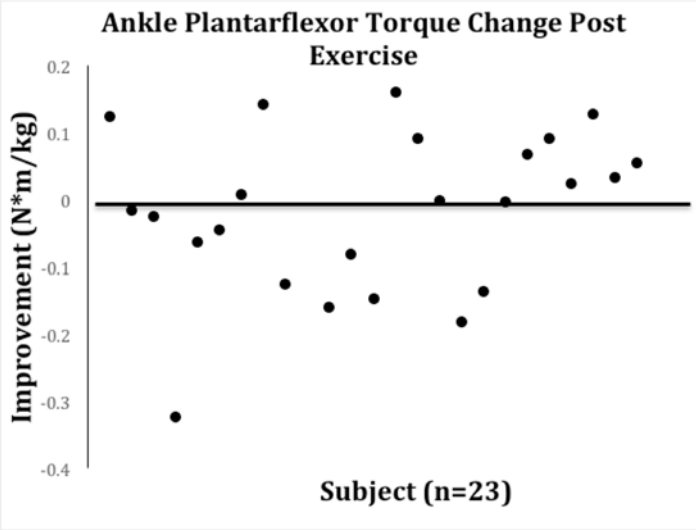

Figure 5. Changes in ankle plantarflexor torque after completing a supervised exercise program in patients with PAD. Fourteen subjects had unchanged or decreased torque values, even though the maximum distance these patients could walk was increased, which shows that treadmill exercise does not improve the ability of muscles with myopathy to produce torque.

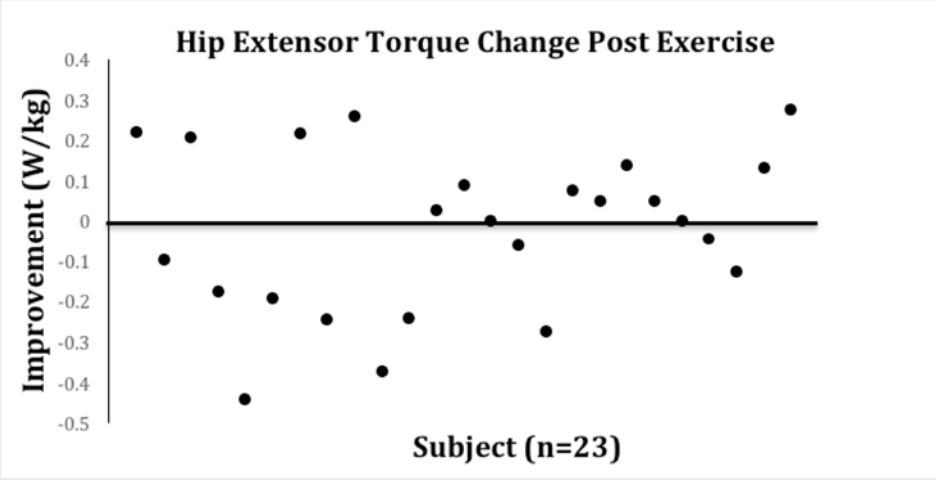

Figure 6. Changes in hip extensor torque following six months of a supervised exercise program demonstrate at least half of the patients have no improvement or further decreased values for torque. Unlike healthy older individuals, patients with PAD still do not redistribute torque from the ankle to the hip, but rather maintain an overall decreased torque profile

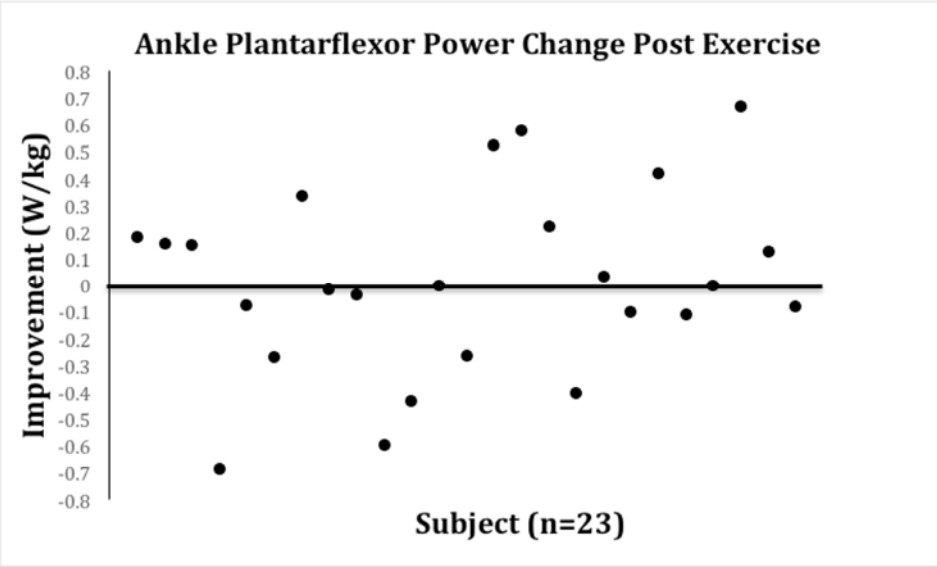

Figure 7. Changes in ankle plantarflexor power of patients with PAD who completed a supervised exercise program. Sixteen subjects had unchanged or decreased ankle power generation, even though the maximum distance these patients could walk was increased, which shows that treadmill exercise does not improve the ability of muscles with myopathy to produce power at the end of the stance phase of walking.

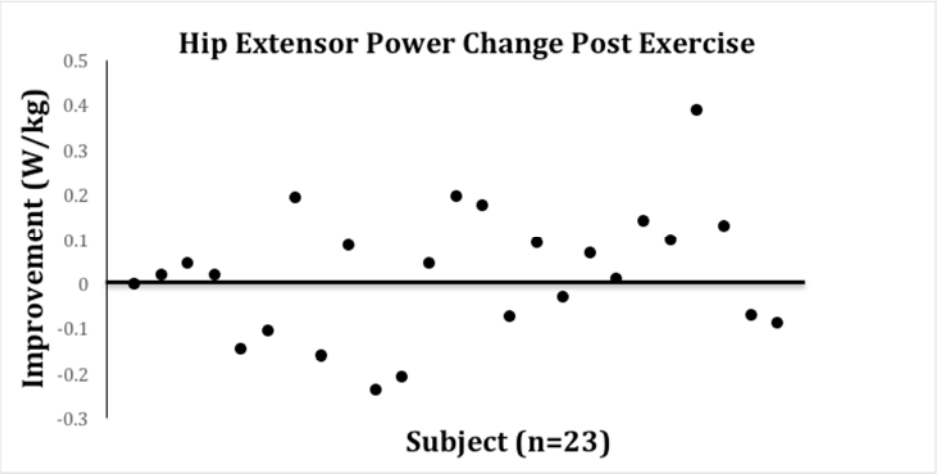

Figure 8. Eleven patients with PAD had unchanged or decreased hip extensor power following the supervised exercise program. These results demonstrate that patients with PAD do not improve ankle propulsion, or redistribute power to the hip even following supervised exercise.

Wearing an ankle foot orthosis immediately improves walking performance in patients with PAD.
Four patients with PAD (Age: 66.0 ± 10.9 years; Body Mass: 84.3 ± 17.1 kg) completed pilot testing of initial and maximum claudication distances while walking with and without an AFO. Patients completed a progressive-load treadmill test[67]. During the treadmill test, the patients with PAD walked on a treadmill that started at 0% grade and 0.83m/sec. Every two minutes, the grade was increased by 2% up to a maximum of 15% grade. The first indication of claudication pain was recorded as initial claudication distance, while the total distance the patients could walk on the treadmill before stopping because of pain was the absolute claudication distance[67]. Throughout the test, we asked the patient to confirm the presence or absence of pain to ensure the

correct initial claudication distance was recorded. We counterbalanced the effect of the AFO by having two patients walk first with the AFO, while the other two walked first without the AFO to prevent a fatigue effect. On average, the patients' initial claudication distance was 140.1 ± 72.5 meters while walking without the AFO and 183.5 ± 121.2 meters while walking with the AFO (Figure 9). The average maximum claudication distance was 366.0 ± 118.3 meters without the AFO and 492.3 ± 66.8 meters with the AFO (Figure 10). Thus, the four patients increased the maximum distanced walked by about 50 meters just by wearing the AFO. These increases in initial and maximum walking distances are comparable to those seen after pharmacotherapy for six months[29, 32].

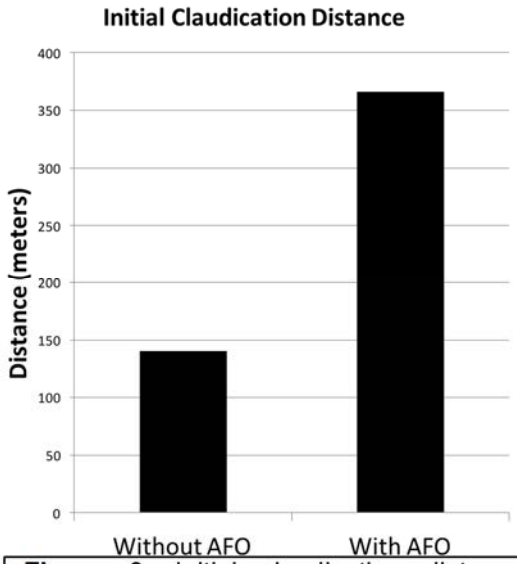

Figure 9. Initial claudication distances improve while walking with an ankle foot orthosis (AFO) compared to walking without an AFO in patients with PAD.

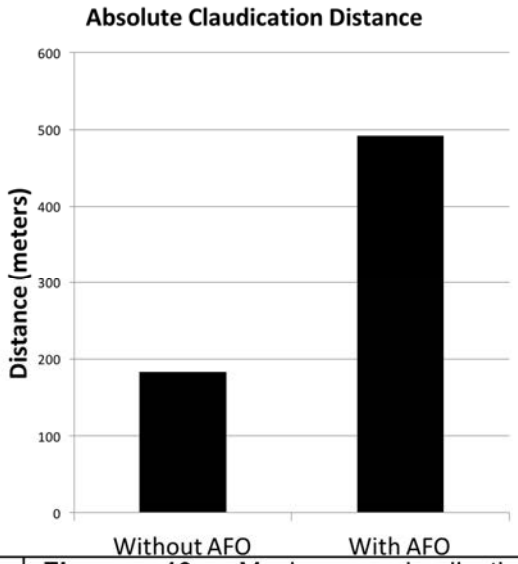

Figure 10. Maximum claudication distances are increased in patients with peripheral arterial disease when walking with an ankle foot orthosis (AFO).

Wearing an AFO trends towards redistribution of torque to the hip in patients with PAD. Four patients with PAD (Age: 60.3 ± 7.21 years; Body Mass: 82.6 ± 18.05 kg) were tested while walking overground with and without the AFO. Peak torque was calculated for the ankle at the end of the stance phase and hip extensor torque was calculated from early stance in each condition. The preliminary results show that the ankle plantarflexor muscles have to contribute less torque to walking while wearing the AFO, as the ankle plantarflexor torque in these four subjects decreased while wearing the AFO (Figure 11; 1.280 ± 0.14 Nm/kg without the AFO and 1.22 ± 0.12 Nm/kg with the AFO). This decrease in ankle plantarflexor torque while wearing the AFO was not expected, but surprisingly, the overall torque profile was also maintained. Thus, our results indicate that walking with the AFO helps patients with PAD in two ways: 1) contributing mechanical torque during propulsion and 2) reducing the demands on the myopathic calf muscles of these patients. The hip extensor torque also increased with the AFO (Figure 12; 0.602 ± 0.12 Nm/kg without the AFO compared with 0.621 ± 0.12 Nm/kg with the AFO). While these increases are small, the fact that all four of the patients actually increased is significant considering that at least 50% of subjects decreased in these same variables following supervised exercise in our preliminary data presented earlier. This subset of preliminary data provides optimism as to the potential of the AFO to improve both walking distances and torque profiles in patients with PAD both acutely, and following a three month AFO intervention.

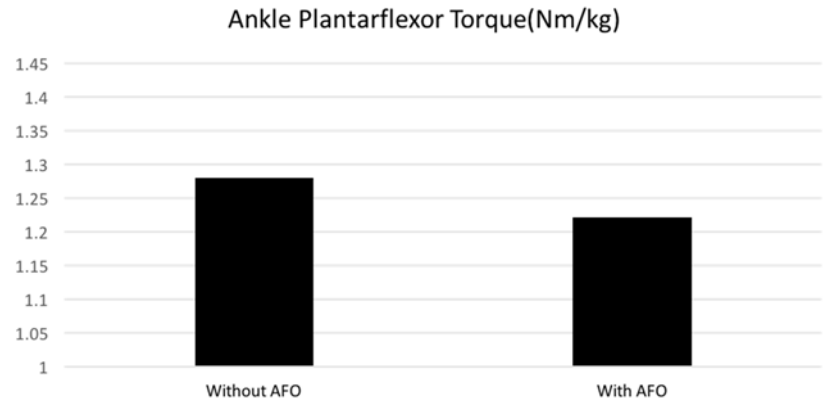

Figure 11. The required torque contribution of the ankle plantarflexors was decreased in four patients with PAD when wearing the AFO. Thus, the AFO contributes mechanical force in place of the ankle plantarflexors and also decreases the oxygen demand by requiring less exertion from those muscles.

Opportunity presented by an ankle foot orthosis (AFO) intervention: Recent studies in healthy and neurological populations have demonstrated that simple AFOs can increase walking performance through reduced energy expenditure[26, 28, 68]. While powered exoskeletons have been a hot-topic in media and pop-culture, clinicians and

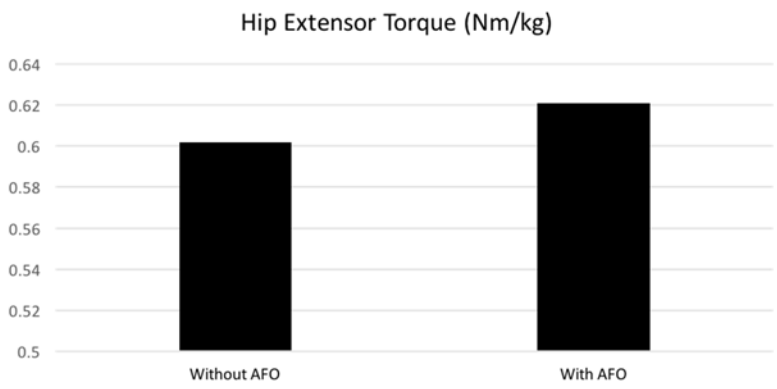

Figure 12. Wearing the AFO allowed four pilot subjects to increase hip extensor torque during early stance, which is consistent with the redistribution of torque from the ankle to the hip seen in healthy older individuals. Utilizing the hip muscles would further decrease the demand on the ankle plantarflexors while walking with an AFO.

scientists are appropriately cautious realizing that such technology is far from being practical and affordable for all individuals who would benefit. However, an off-the-shelf AFO is the least complex form of exoskeleton, that is easily adjustable, affordable, and available to immediately be prescribed and worn by patients with PAD wishing to walk further who do not wish or are not candidates to undergo an operation.

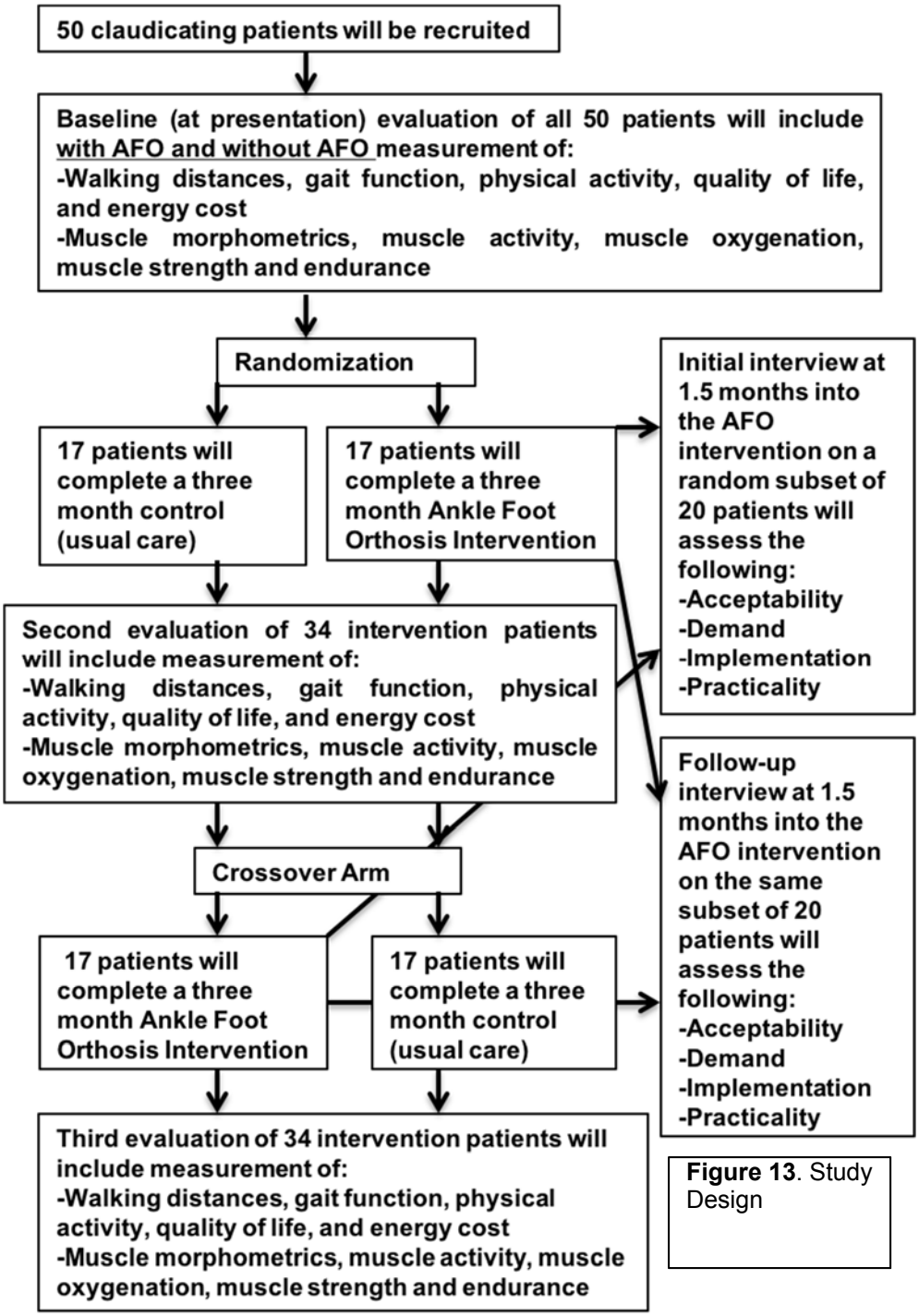

Figure 13. Study Design

Research Plan

Study Design: We plan to recruit 50 patients with PAD from the claudication clinic at the Nebraska and Western Iowa Veterans Affairs' Medical Center (VAMC) in Omaha, Nebraska (Figure 13). As we just completed enrollment of a five-year NIH grant that included 200 patients (R01 AG034995) and have collected over 50 patients in 18 months for a COBRE research project (P20 GM109090), we expect this recruitment goal to be attainable. The collaborating vascular surgeons, Drs. Johanning and Pipinos, will evaluate all patients seen at the University of Nebraska Medical Center and Veterans' Affairs Medical Center claudication clinics. The PI also participates in these clinics and works side by side with the surgeons.

Inclusion criteria: At entry into the study, all subjects must:

1) be able to give written, informed consent

2) demonstrate positive history of chronic claudication

3) demonstrate exercise-limiting claudication established by history and direct observation

during a screening walking test administered by the evaluating vascular surgeon.
4) have an ankle/brachial index < 0.90 at rest[69]
5) and have a stable blood pressure regimen, stable lipid regimen, stable diabetes regimen and risk factor control for 6 weeks.

Exclusion criteria: Any potential subjects will be excluded if they have:
1) rest pain or tissue loss due to PAD (Fontaine stage III and IV)[69]
2) acute lower extremity ischemic event secondary to thromboembolic disease or acute trauma
3) walking capacity limited by conditions other than claudication including leg (joint/musculoskeletal, neurologic) and systemic (heart, lung disease) pathology

Specific Aim 1: Determine the acute impact of the AFO on walking performance

Approach: We propose to study 50 patients with PAD, measuring walking performance with and without wearing a carbon composite AFO. Patients will wear the AFO on the affected leg(s), so patients with bilateral leg symptoms will wear them on both legs while patients with unilateral disease will wear the AFO on the symptomatic leg only. Walking performance will include measurement of initial and absolute walking distances, and lower extremity torque and power. Energy cost and muscle activity will be tested as potential mechanisms contributing to improvement in walking performance. Conditions will be randomized, with half of the subjects performing the tests without the AFO and the other half starting with the AFO walking conditions. All data will be collected in the Biomechanics Research Building (BRB). All subjects will be consented after reporting to the BRB and the outcomes detailed below will be assessed. The entire process is expected to take 2.5 hours.

Outcomes
1) **Initial and absolute walking distances:** Walking distances will be determined with a progressive-load treadmill test[67] with initial and maximum claudication distances as outcomes. During the treadmill test, patients with walk on a treadmill that starts at 0% grade and 2.0 mph. Every two minutes, the grade will be increase by 2% up to a maximum of 15% grade, and the speed held constant throughout the test[67].
2) **Lower extremity torque and power:** Biomechanical data will be collected using eight in-ground AMTI force platforms and a 12 camera high speed digital motion capture system (Cortex 5.1, Motion Analysis Corp, Santa Rosa, CA) to collect three dimensional kinematics (60 Hz) and kinetics (ground reaction forces, 600 Hz). Reflective markers will be placed at specific anatomical locations on the lower limbs, utilizing the marker systems of Vaughan[70] and Nigg[71]. Following the setup, kinematics and ground reaction forces will be recorded while the subjects walk with their self-selected pace through a ten-meter pathway. Each patient will be tested before the onset of claudication pain (pain free) with a mandatory one-minute rest period between the walking trials to insure that all trials are in a pain free condition. A total of five walking trials per leg will be collected. Following the collection of overground data, the patients with PAD will be allowed to rest.

   Data are exported and processed in custom laboratory software using MATLAB (Mathworks Inc., MA) and Visual 3D (C-Motion, Inc., MD). This software is used to calculate ground reaction forces for the vertical, anterior-posterior, and medial-lateral direction, and joint angles and joint angular velocity for the hip, knee, and ankle during the stance phase of walking. Lower extremity joint muscular responses and contributions during walking are determined using joint torques and powers. Joint torques and powers are calculated using inverse dynamics for the hip, knee, and ankle during the stance phase of walking. Inverse dynamics combine the kinematics and the ground reaction forces as described by Winter[72]. Additionally, spatial and temporal characteristics will be calculated using custom code in MATLAB (Mathworks Inc., MA). From this data our primary lower extremity function outcome measures will be ankle and hip plantarflexor torque and power, although all kinematic and kinetic measures of the lower extremity will be investigated.
3) **Muscle activity:** Electromyographic data will collected from the gasctrocnemius and soleus muscles of the affected legs at 1000 Hz using surface electrodes with the DelSys Trigno™ wireless system. Prior to the trials maximum voluntary contraction electromyographic signals will be recorded for each muscle via isometric contraction for three seconds. For electromyographic data analysis, time-domain and frequency-domain analyses will be performed using custom Matlab programs. Time-domain analysis of electromyographic signal provides a measure of the average muscle activity and work produced by a given muscle (activation profiles)[73]. The mean electromyographic signal (EMG_{mean}) will be computed to measure the average muscle activity for each trial. The electromyographic envelope (EMG_{env}) will also be calculated by integrating the time series of root-mean-square electromyographic signal for each trial. EMG_{env} provides a measure of the muscle work for a given trial. Frequency-domain analysis of

electromyographic signal provides a window into muscle fatigue and motor unit recruitment [73]. The raw electromyographic signal will be converted to the frequency domain using a Fast Fourier Transform to determine the power spectrum. Median frequency and frequency bandwidth will be computed from the power spectrum. Median frequency will be computed as the frequency at half of the integrated power spectrum as given by the following equation (1) [73]:

$$\int_0^{f_{med}} P(f)df = \int_{f_{med}}^{f_{\max}} P(f)df \quad \int_0^{f_{med}} P(f)df = \int_{f_{med}}^{f_{\max}} P(f)df \tag{1}$$

where P(f) is the power at frequency f, f_{med} is the median frequency, and f_{max} is the maximum frequency of the power spectrum. Frequency bandwidth (f_{band}) is the difference between the highest and lowest frequency where the power exceeds half the maximum power of the power spectrum.

4) **Energy cost:** A portable metabolic cart (Cosmed K4b2, Cosmed USA Inc., Chicago, IL), will be used to measure gas exchange on a breath-by-breath basis, providing a measure of oxygen consumption. Steady-state oxygen consumption in ml/kg/min will be calculated during the walking distance test.

Statistical analysis: The sample size was calculated to detect effect sizes observed in pilot data for initial and absolute walking distances. The mean (SD) difference in initial walking distance with and without AFO was 43.4 meters (93), corresponding to a standardized effect size of 0.47 standard deviations. A sample size of 50 subjects will provide 84% power to detect differences of 0.47 standard deviations between walking with and without an AFO, using a paired t-test for sample size estimation purposes only, and a significance level of 0.02 to informally adjust for multiple testing. The standardized effect size for absolute walking distance was 1.29 standard deviations, so the sample size of 50 subjects will also provide sufficient power to detect this difference. For statistical analysis, a linear (or generalized linear, as appropriate) mixed modeling approach will be used. This approach will allow us to detect differences between walking with and without an AFO while adjusting for confounding variables. The level of significance will be set at 0.05.

Expected results/possible limitations: Based on work with AFO devices in other pathological populations, we expect the AFO will improve lower extremity torque and power generation enough to demonstrate a clinically important difference. If our hypothesis is correct, the AFO will be a potential new conservative intervention for improving walking performance in patients with PAD, along with the mechanisms contributing to those improvements. If our hypothesis is not supported, we speculate that the AFO may still be a viable conservative treatment option based on results of Specific Aim 2. For example, the AFO may improve walking performance over the course of the three-month intervention. This aim will also provide data on muscle contribution that could be used to design and test an improved AFO. Our preliminary work looks promising for increasing the distance that patients with PAD can walk. Completion of this aim will provide the groundwork for exploring and designing even more effective AFO devices.

<u>Specific Aim 2: Determine improvements in walking performance following a three month AFO intervention</u>

Approach: We propose to study a subset of 30 patients from Specific Aim 1 measuring walking performance, physical activity, and quality of life after a three-month AFO intervention. Walking performance will be assessed in the same manner as in Specific Aim 1 during the baseline assessment. Physical activity will be assessed using accelerometers while quality of life will be assessed through questionnaires. To investigate mechanisms contributing to improvements in walking performance, physical activity and quality of life, we will measure changes in energy cost, muscle morphometric parameters, muscle oxygenation, and muscle strength and endurance at baseline and following each of the three month intervention arms (control and AFO).

AFO and Control Intervention: Patients will be asked to wear an AFO each day for three months. Subjects will have an off-the-shelf AFO (Figure 2) chosen initially based on shoe size and adjusted or exchanged for a different size during the initial evaluation after entering the study. The patients will be asked to wear the AFO at all times except when they are in bed or showering/bathing. The instructions given to the patients about walking will be the same as typically provided by clinicians, which is to walk 30 minutes per day, most days/week. We have chosen this specific AFO device because it is already available for use in a clinical environment, is composed of a carbon-composite material that will capture and return energy during the gait cycle, and has successfully contributed to propulsion during walking in other clinical populations[26, 28]. Patients will be able to contact the nurse coordinator at any time if they need the AFO adjusted or have questions about what should happen during the intervention. Subjects in the control arm will be asked to continue the same lifestyle for three months. The intervention arm order will be randomized (see Statistical Analysis)

Outcomes: All outcomes will be assessed at baseline and following each arm (control and AFO).

1) **Initial and absolute walking distances, 2) Lower extremity torque and power**, **3) Muscle activity, and 4) Energy cost will all be measured as described for Specific Aim 1.**
5) **Physical Activity:** Participants will wear the Actigraph (Actigraph GT3X, Actigraph, FL, USA) accelerometer on their hip for seven days (the whole day except when sleeping) prior to starting the AFO intervention to measure baseline activity level. The accelerometer will be mailed back to researchers in a pre-paid envelope. Two weeks prior to the post-intervention visit to the laboratory, an accelerometer will be mailed to participants to wear the final seven days before the visit. Average steps/day, maximum cadence, and average peak activity index will be calculated.
6) **Quality of Life:** The Walking Impairment Questionnaire[74], Medical Outcomes Short Form 36, and Edinburgh Claudication Questionnaire will be used to assess quality of life. The Walking Impairment Questionnaire has been validated in patients with claudication[74] and the Short Form 36 has been extensively evaluated and tested with a variety of populations and is able to distinguish between groups of varying health status[75, 76]. The Edinburgh Claudication Questionnaire was developed in an iterative, systematic fashion and has been implemented as a more holistic approach to identify presence of intermittent claudication in many clinical trials.[20, 77-82]
7) **Morphometric parameters:** An ultrasound transducer (LS128 CEXT-1Z, Telemed, LT, Lithuania) will be used to assess thickness of the plantarflexor muscles using a standard real time B-mode image. Muscle thickness will be measured on the posterior medial and lateral surfaces, 20, 30, and 40% between the lateral malleolus of fibula and the lateral condyle of the tibia. The average values of muscle thickness at all measured sites will be the primary outcome measure.
8) **Muscle Oxygenation:** Continuous-wave near infrared spectroscopy (Moxy Monitor, Fortiori Design LLC, MN, USA) will be measured bilaterally on the gastrocnemius calf muscle before, during and after the walking distance test. We will measure resting StO_2, minimum StO_2 during the maximal treadmill test, time to minimum StO_2, and the StO_2 recovery time.
9) **Muscle Strength and Endurance:** An isokinetic dynamometer (Biodex 4 Medical Systems, Inc. USA) will be used to measure peak isokinetic strength (torque) of the ankle and hip of the more symptomatic leg. Peak torque and total work performed for ankle plantarflexion, ankle dorsiflexion, hip flexion, and hip extension will be measured. Subjects will perform one trial of five repetitions at 60 degrees/second to assess strength, and one trial of 15 repetitions at 120 degrees/second to assess endurance.

Statistical analysis: A portion of patients from Aim 1 will be randomized to one of two intervention arms (control then AFO, or AFO then control). We expect differences from a 3-month training to be larger than the immediate differences shown in Aim 1. A sample size of 30 subjects (15 per treatment arm) will provide 80% power to detect differences of 0.59 standard deviations between walking with and without an AFO, using a paired t-test for sample size estimation purposes only, and a significance level of 0.025 to adjust for multiple testing. This sample size will also allow us to detect an effect size of 1.2 for differences between the two groups at each time point. Assuming a 10% drop-out rate, we will randomize 17 per group, for a total of 34 subjects. For statistical analysis, a linear mixed modeling approach (or generalized linear mixed model, as appropriate) will be used. This approach will allow us to detect differences within and between groups, and adjust for confounding variables. The main comparison of interest will be changes in walking distances due to wearing the AFO. The use of the crossover design will allow us to investigate several questions of interest: 1) If walking distances improve after wearing the AFO for 3-months; 2) If walking distances worsen over the first 3 months for subjects not wearing the AFO in the first period; and 3) If the improvement in walking distances from wearing the AFO for three months is retained over the second 3 months (no AFO). To evaluate the relationship between improvements in walking performance, physical activity, and quality of life, and improvements in morphometric parameters, muscle oxygenation, and muscle strength and endurance, multiple correlations will be used. The level of significance will be set at $p=0.05$.

Expected results/possible limitations: We hypothesize that an AFO intervention will increase walking performance, physical activity levels, and quality of life through improvements in the function of the muscles of the treated legs. If our hypothesis is correct, the AFO intervention is a new effective conservative intervention for patients with PAD. Because the premise is that the AFO will maintain overall torque and power while requiring a lower contribution from the leg muscles of patients, the patients will be able to walk further, placing less stress on their leg muscles, thereby allowing regeneration of structure and function of the muscles. Another possibility is that the patients experience an improvement in their walking performance, physical activity levels and quality of life but do not see improvements in muscular function of the legs. In this case, the

AFO would still be beneficial for patients to use. However, if none of the components of our hypothesis are correct, and neither the function and quality of life nor the muscle characteristics improve despite conscientious use of the AFO, then our study would direct us away from AFO-type treatments and towards other therapies and rehabilitation geared towards muscle health.

Specific Aim 3: Determine the feasibility of a three month AFO intervention

Approach: We will utilize Bowen and colleagues' standards for feasibility studies to measure the feasibility of using an AFO over three months in a random subset of 20 patients from Specific Aim 2. We will employ interviews and surveys throughout the three-month AFO intervention period to assess the following outcomes.

Outcomes

1) **Acceptability:** Interviews and a satisfaction survey will be implemented to assess satisfaction of using an AFO, intent to continue use, and perceived appropriateness measured. The research team will conduct interviews at 1.5 months, and three months. Interviews will last no longer than 30 minutes and will take place at the UNO Biomechanics Research Building. Satisfaction surveys for all participants will be completed during the final assessment in the Biomechanics Research Building.
2) **Demand:** Actual use and perceived demand will be measured using an accelerometer and interviews. An additional accelerometer will be given to the patient at the baseline visit. Battery life on these accelerometers can span over 30 days, especially with a lower sampling frequency of 1 Hz. Each month a new accelerometer will be mailed to participants and the package will include a pre-paid mailer for subjects to return the previous accelerometer for downloading data and charging. Additionally, patients will be contacted randomly three times during the 3-month study period to further assess the actual use. Perceived demand will be assessed via interview at baseline and at three months.
3) **Implementation:** Degree of use, success/failure of use, and factors affecting the ease/difficulty of use will be measured using interviews to determine implementation. Interviews will take no longer than 30 minutes and will occur at 1.5 months and 3-month time points.
4) **Practicality:** Measurements of the positive/negative effects of the AFO and ability of participants to effectively use the AFO will be made to determine the practicality of the intervention. We will assess these factors via interviews at three months.

Analysis for Specific Aim 3, Outcomes 1-4: Data from interviews will be transcribed and analyzed by the research team in NVivo 10 (QSR International Pty Lid., Victoria, AU). Researchers will independently code transcripts and meet to reach agreement on major data themes. Emerging themes will be identified using a constant comparison approach. This approach allows for the development of explanations through patterns but also allows the coder to harness theory and prior knowledge or research to answer research questions.

Statistical analysis: Descriptive statistics will be used to summarize results of survey data. We will use counts and percents for categorical data, and means and standard deviations for quantitative data. Associations between walking distance variables and acceptability, use, and practicality variables will be examined using t-tests for dichotomous variables and correlations for continuous variables.

Expected results/possible limitations: We expect that an AFO intervention will be feasible to implement for three months in patients with PAD. If our hypothesis is correct, the study will establish the AFO as a new intervention that will likely be easily adopted by patients. It is also possible that the intervention does not prove feasible in one or more areas. If that happens, the study results will provide specific information on which aspects of the application of AFO treatment are not feasible. Those area(s) can then be further evaluated and potentially improved. Importantly, the results will inform the importance of these areas to feasibility of all interventions for the PAD patient group, not just the AFO intervention proposed in the current study.

Table 2: Project Timeline	1st Year	2nd Year	3rd Year	4th Year	5th Year
Subject recruitment	XXXXXX	XXXXXX	XXXXXX	XXXXXX	XXX
Baseline assessment	XXXX	XXXXXX	XXXXXX	XXXXXX	
AFO and Control Intervention Arms	XXX	XXXXXX	XXXXXX	XXXXXX	XXX
Post AFO and Control assessments	XX	XXXXXX	XXXXXX	XXX	XXX
Data analysis		XXXXXX	XXXXXX	XXXXXX	XXXXXX
Abstract/manuscript development		XXX	XXXXXX	XXXXXX	XXXXXX
Grant writing				XXXXXX	XXXXXX

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