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Improving Walking in Peripheral Artery Disease ClinicalTrials.gov Identifier (NCT Number): NCT05103280

VA Tennis Shoes Protocol

Title: Improving Walking in Peripheral Artery Disease, Using Specially Designed Assistive Shoes

Objective: The objective of this research is to evaluate the ability of different ***specially designed tennis shoes*** to improve walking performance, muscle oxygenation of patients with peripheral artery disease (PAD).

Hypothesis: We hypothesize that the specially designed tennis shoes will provide assistance to the ischemic legs of patients with PAD and will therefore reduce the biological contribution and oxygen requirements of the ischemic leg muscles. This will acutely increase the walking performance, muscle oxygenation in the patients.

If our hypothesis is correct, the carbon fiber insole shoes and spring shoes may become a new effective conservative intervention for patients with PAD. However, if none of the components of our hypothesis are correct, then our study would direct us away from the carbon fiber insole shoes and/or spring shoes and toward other therapies.

We also hypothesize that an intervention with specially designed tennis shoes (spring loaded or carbon fiber insole shoes) will increase physical activity, and improve walking performance and quality of life. Our preliminary results show promising results in increasing the walking distances including initial claudication distances and absolute claudication distances during first-time use of the specially designed tennis shoes. Subjects will complete a 3month intervention with their preferred specially designed tennis shoe based on the initial data collection. They will be tested prior to starting the intervention and after 3 months of the intervention.

Endpoints measured: The patients will walk while wearing their own walking shoes, the carbon fiber insole shoes and the spring-loaded shoes (in random order) and we will measure the following performance endpoints for both phases:

1) **Initial and maximum claudication distance on our instrumented treadmill using the Gardner protocol:** Subjects will complete a Gardner treadmill walking. Subjects will walk in a dynamic gait and pressure analysis treadmill (FDMT Scifit AC500M, Noraxon USA,Inc., Scottsdale Ariz) located at the VA Medical center at Omaha. This treadmill collects synchronized pressure measurements allowing for gait analysis and the calculation of steps taken during exercise. Participants initiated exercise at 2.0 miles per hour at 0.0% incline. With each subsequent 2-minute stage, the treadmill incline was increased 2.0% to a maximum of 12.0%. Time of initial symptoms (claudication onset time [COT] and time at which claudication symptoms were prohibitive to further walking [peak walking time] will be recorded. Data will be collected using regular shoes and specially designed (carbon fiber insole shoes and spring) shoes. They will be allowed to rest for 15 minutes between tests. Patients will do 3 walks in the treadmill (regular walking shoes, carbon fiber insole shoes, and spring shoes).

2) **Calf muscle saturation at one-minute walking:** Bilateral gastrocnemius muscle oxygenation (StO2) will be measured using continuous-wave near infrared spectroscopy (PortaMon, Artinis Medical System, Netherlands) before, during and after each treadmill walking condition (described above). Measurements will be continuously captured during the exercise and recovery interval. We will measure resting StO2 and StO2 at 1-minute walking.

3) **Vertical ground reaction forces in the first two minutes of walking:** Biomechanical data will be collected with a dynamic gait and pressure analysis treadmill (FDMT SciFit AC5000M, Noraxon USA, Inc.). The parameter measured will be the vertical ground reaction force.

4) We will use the Borg Rating of Perceived Exertion (RPE) questionnaire after each condition

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 intervention phase to measure baseline activity level and seven days after the intervention phase to measure post-intervention physical activity. Average steps/day, maximum cadence, and average peak activity index will be calculated.

6) **Questionnaires:** At the end of the study subject will be interviewed and asked to fill out survey questionnaires to assess acceptability, demand, implementation, and practicability. This interview will be held via phone call.

Research Design: This study will be a prospective clinical trial.

Background: Peripheral Arterial Disease (PAD) affects approximately 8.5 million of people age 40 and older in the United Stated according to the CDC (Benjamin 2019). Intermittent claudication (IC) is the most common presentation of PAD. Intermittent claudication presents as cramping pain, occurring in the calves, thighs and/or buttocks brought on by physical activity and relieved with rest (Myers 2016). This impairment is of major importance primarily because it restricts the physical activity of PAD patients, leading to further adverse effects on their general health and quality of life (Hernandez 2019). Recently IC has been identified as an ambulatory disorder. Previous studies done by our group demonstrate that patients with clinically diagnosed femoro-popliteal PAD have significant ankle motion alterations with abnormal ankle joint kinematics. Celis et at demonstrate that PAD patients had evidence of significant ambulatory abnormalities even when not experiencing any claudication pain. The abnormalities contributing to the baseline gait dysfunction are complex and include axonal nerves loss (Koopman1996)(Laghi1996) and mitochondrial dysfunction (Pipinos2007)(Pipinos2006)(Pipinos2000). Ischemia superimposed to this issue would then result in variability worsening gait resulting in an increased work requirement and energy cost.

Despite the functional limitations present in PAD, only few medical therapies exist for improving walking performance and preventing mobility loss in patients with PAD. Exercise training has been demonstrated to improve PAD symptoms and is recommended as first line therapy for PAD. The carbon fiber insole tennis shoe is designed with a full-length, carbon fiber plate underfoot that is supposed to provide a propulsive sensation to help to push the pace. Hoogkamer et al reported that this tennis shoe lowered the energetic cost of running by 4% on average (Hoogkamer 2018). The spring-loaded shoe has a shock-absorbing springs in the soles that relieve the stress and fatigue from athletic activities. In this study, we want to evaluate the effectiveness of these two specially designed tennis shoes and determine if they improve walking performance and/or reduce walking work requirement in PAD patients compared to regular walking shoes.

Methodology:

Recruit 30 willing patients with peripheral vascular disease and claudication at the vascular surgery clinic at the Nebraska and Western Iowa Veterans Affairs Medical Center (VANWIHCS) in Omaha.10 patients will be recruited from the total 30 patients for the intervention phase and rest of the 20 patients will only participate in the baseline phase . Patients will be evaluated by a Board-Certified Vascular Surgeon to determine if they have PAD and whether they are eligible to participate in the study the study. Subject will be consented prior to the study.

1. Inclusion/Exclusion Criteria
   Inclusion criteria: At entry into the study, all subjects must:
   a. Be able to provide written, informed consent
   b. Demonstrate positive history of chronic claudication
   c. Demonstrate exercise-limiting claudication established by history and direct observation during a screening walking test administered by the evaluating vascular surgeon
   d. Have an ankle/brachial index <0.90 at rest
   e. 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:

   a. Rest pain or tissue loss due to PAD (Fontaine stage III and IV)
   b. Acute lower extremity ischemic event secondary to thromboembolic disease or acute trauma
   c. Walking capacity limited by conditions other than claudication, including leg and systemic pathology
2. Patients will perform Gardner protocol on the pressure treadmill at the VA at Omaha, NE.
   a. Normal walking shoes

   b. Carbon fiber insole shoes
   c. Spring loaded shoes
3. Clinical data to be collected
   a. ABI
   b. Medical conditions/comorbidities

4. Voluntary Data Repository- If the patient agreed a study and health data will be de-identified and store in a special VA research drive only available to authorized research personnel. Information will be used for future studies about PAD or other vascular diseases. If the patient agrees he will be asked to sign a special HIPPA form.

Statistical Analysis: The sample size was calculated to detect effect sizes observed in pilot data for ankle plantarflexor push off. A sample size of 30 subjects will provide 79% power to detect differences of 0.30 standard deviations between walking with control and assistive tennis shoes, using a paired t-test for sample size estimation purposes only, and a significance level of 0.02 to informally adjust for multiple testing. 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.

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 performance and comfort, fatigue, perceived intensity, and feasibility variables will be examined using t-tests for dichotomous variables and correlations for continuous variables. Comparisons will be done independently for each shoe type.

We expect differences from a 3-month intervention to be larger than the immediate differences shown in Aim 1. A sample size of 30 subjects would provide 80% power to detect differences of 0.59 standard deviations between walking with and without assistive tennis shoes, using a paired t-test for sample size estimation purposes only, and a significance level of 0.025 to adjust for multiple testing. For this pilot study, we plan to collect 10 subjects after the intervention and seek additional funding to fully power the study.

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 (different types of assistive shoes), and adjust for confounding variables. The main comparison of interest will be changes in walking distances due to wearing the assistive shoes. This pilot study will allow us to detect if walking distances improve after wearing the assistive shoes for 3-months. To evaluate the relationship between improvements in walking performance, physical activity, and quality of life, multiple correlations will be used. The level of significance will be set at p=0.05.

Outcome measure	Mean 1	Mean 2	Difference	Standard Deviation	Power	Required Sample Size
Push-off[11]	1.4	1.7	-0.3	0.30	0.79	29
Visual analog scale[12]	5.0	7.0	-2.0	2.00	0.81	30
Borg (scenario 2)[13]	14.0	11.0	3.0	2.50	0.81	23

Assumptions for sample size calculations to obtain 80% power. The test statistic is a two-sided paired t-test with an assumed correlation between mean 1 and mean 2 of 0.30. The alpha level is assumed as 0.001 to account for multiple comparisons between the different shoe types. Mean 1 is assumed as normal walking the control shoe and mean 2 is walking in the best assistive shoe. Choosing the largest sample size across all measures will ensure the desired power for all outcome measures*[14].

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