Post-revascularization rehabilitation to improve function in Veterans with peripheral arterial disease (PAD)

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STUDY PROCEDURES:

INTERVENTIONS

1. Active Exercise Training: All participants who are in the exercise program will exercise for approximately 3 months, 3 times per week at the Baltimore VA Medical Center Annex, or the VA Medical Center. These exercise sessions will be supervised by exercise physiologists or trained staff. The aerobic exercise training program will include a warm up followed by 30-45 minutes of cumulative walking on a treadmill or around a track. Individuals will initially begin walking for 10-15 minutes per exercise session (depending on tolerance) and will progress weekly until 30-45 minutes of cumulative walking has been achieved. For individuals who experience claudication pain, they will be asked to walk until the claudication pain reaches a 3 on a 0-4 scale (0= no pain, 1 = onset of pain, 2 = moderate pain, 3 = intense pain, and 4 = maximal pain) after which they will rest. They will then be asked to walk again. This pattern of intermittent walking will be continued until the prescribed number of minutes of walking is met. Subjects will also be asked to walk at home on days they do not perform supervised exercise. Participants may also participate in strength training (ST) during the same session. This will consist of training of the knee extensors, knee flexors, plantar flexors and dorsiflexors. Subjects will perform approximately 1-3 sets of 4-15 repetitions for each exercise as tolerated. Training may be performed on Keiser K-300 air powered machines utilizing pneumatic resistance (Leg Extension Machine, Leg Curl Machine, Leg Press Machine) or with resistance bands or tubes. Each session of ST will take approximately 15-30 minutes. Blood pressure and heart rate will be assessed before and after each session. If the participant has type 2 diabetes and is on medications that may result in hypoglycemia, we will monitor blood glucose levels before and after exercise.

2. Passive Exercise Training (NMES): Neuromuscular electrical stimulation (NMES) will be used to electrically induce contraction of the plantarflexors and dorsiflexors of both lower extremities. The protocol will employ an FDA cleared device for this purpose. NMES is routinely used in clinical care and has been used in other studies at UMB. Our specific protocol will require the application of NMES units on each lower extremity. Electrodes will be placed over the plantar and dorsiflexors of each leg. The stimulator's parameters setting will be adjusted to elicit contraction while maintaining participant comfort. Stimulation will be provided for approximately 15-30 minutes daily as tolerated by the participant.

TESTING PROCEDURES:

*Based on each subject's schedule and availability, the Principal Investigator or clinical investigative team may choose not to perform every research procedure described below. If this occurs it will be noted in the participant research notes. Participants may also be asked to repeat one or more of the research tests should it be necessary due to a technical error in its performance and/or measurement, an inadequate sample is obtained for analysis, or there was an unforeseen problem with data collection.

1. Blood Sampling: Blood plasma and/or serum will be used to measure cardio-metabolic and angiogenic factors (growth factors, inflammatory cytokines, cardio- metabolic risk factors, and markers of nutritional status). We may also measure endothelial progenitor cells, new hormones, inflammatory proteins and biomarkers as other technologies for measuring biomarkers of cardiovascular disease are identified. We will store plasma and serum and blood

cells for analysis at a later time. These samples will be de-identified. Genetic testing will also be performed on blood samples.

2. Treadmill Exercise Test: The tests described below will be supervised by staff clinicians with the assistance of CPR-trained study team members. Subjects will walk on a treadmill at approximately 2mph and grade is increased every 2 minutes until the subject cannot continue. Subjects will wear a mask with a mouthpiece that will collect expired air for measurement of ventilated gasses. Subjects are instructed to report the onset of claudication pain and then to walk as long as they can endure the pain (at which time the test will end). Heart rate and ECG are monitored continuously; arm and ankle blood pressure is monitored intermittently throughout the protocol using either auscultation or Doppler ultrasound. Cardiac output (PhysioFlow Enduro) and calf muscle oxygen saturation (Oxiplex TS near-infrared spectroscopy) may also be non-invasively measured during the test. Exercise tests may be stopped if the subjects indicate they are unable to continue or they experience any of the following: chest pain, dizziness, faintness, fatigue, pallor, cyanosis, cardiac arrhythmias or decompensation, or severe hyper-or hypotension (American College of Sports Medicine 2006.Guidelines for Exercise Testing and Prescription 7th ed.). Subjects may be asked to repeat this test while wearing a NMES unit. During Phase 3 & 5 this test will be performed twice. Once to establish any improvements in how long the patient can walk they will be asked to walk as long as possible. The second test will be submaximal and will be terminated when the patient reaches the same time and grade completed in a previous research testing phase. The submaximal test will be supervised by a CPR-trained exercise physiologist.

3. Strength Testing: A) Muscular strength (leg extension, leg press, and/or leg flextion) will be measured by 1-repetition maximum (1RM) testing on Keiser K-300 air powered machines or a Biodex strength testing system. Participants will complete a brief, low-intensity warm-up prior to the test. Participants will be asked to perform exercises against a gradually increasing resistance after each successful exercise repetition until the maximal load is obtained. They will be perform multiple trials (typically ~3-7) with ~ 1 minute of rest between trials. B) Plantar and dorsiflexion will be measured using a hand-held dynamometer or with the Biodex strength testing system. Participants will be properly stabilized to ensure minimal movement artifacts. Additionally, verbal encouragement will be provided during task to encourage maximal volitional contraction.

5. Functional Tests and Questionnaires: The physical performance tests include the Modified Physical Performance Test [standing balance, chair rise, book lift, put on and remove jacket, pick up a penny, turn 360 degrees, 50-foot walk, stair ascent/descent, self-selected gait speed (8-foot walk)], grip strength, balance, and the 6-minute walk. We will also administer questionnaires (attached) including the Walking Impairment Questionnaire (WIQ), SF-36, the Life Space Questionnaire, and the Vascular Quality of Life (VascuQoL). Participants may be asked to repeat these tests while participating in the intervention so that we may assess interim efficacy.

6. Body Composition: Total and regional fat mass, lean tissue mass, % body fat, bone mineral content, and bone density will be determined by dual-energy x-ray absorptiometry (DXA). Computed tomography scans of the abdomen and leg are done to quantify regional fat and muscle distribution. The DXA and CT scans are performed by radiology technicians. [*DXA and CT scans will only be performed during post-revascularization testing (Phase 3) and 3-month testing (Phase 5).] We will also measure body circumferences with a tape measure.

7. Ultrasound Testing: This test may be performed before and after exercise. Doppler ultrasound non-invasively visualizes anatomic structures and determines intra- arterial blood flow. The test may be performed at the Vascular Laboratory at the University of Maryland Medical Center. Subjects will be positioned on a cushioned table and gel will be applied to their skin. An ultrasound transducer will be moved over the areas of the body being imaged. Contrast-enhanced ultrasonography will be employed to improve visualization. This involves the administration of stabilized microbubbles, an ultrasound contrast agent via a peripheral intravenous line. Participants will undergo the ultrasound testing before and after a walking on a treadmill for approximately 10 minutes.

STATISTICAL ANALYSIS:

We will use exploratory data analyses to review our data looking for extreme values which will be checked for transcription or other errors. Because our outcome measures will be measured multiple times, our intent is to use repeated measures ANOVA to compare outcome measures among treatment and control. However, as this is a pilot study designed to demonstrate proof of concept and to generate data with which to make accurate power calculations, we may initially analyze within-group changes using paired t-tests and among-group differences with independent samples t-tests.