Intermittent pneumatic compression to improve the outcome of revascularization for severe peripheral artery disease: a pilot study

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1.0 Background

Peripheral artery disease (PAD) is characterized by atherosclerotic obstruction of the arteries in the lower extremities and affects approximately 10% of individuals older than 65 years. Patients with symptomatic PAD experience walking impairment and declines in physical performance and quality of life. At the extreme end of the clinical spectrum, patients with critical limb ischemia (CLI) have ischemic pain at rest and develop nonhealing or gangrenous wounds that might necessitate limb amputation. These patients with severe PAD require comprehensive medical management and effective limb revascularization to augment tissue oxygenation, promote wound healing and reduce pain. Endovascular and surgical interventions are considered in patients with PAD who have developed lifestyle-limiting claudication no longer responsive to conservative therapy and CLI. Patients with symptomatic PAD receiving intensive evidence-based therapies undergo peripheral revascularization frequently, with approximately 1 in 5 (19.3%) undergoing procedures at 3 years. Despite major technological advances in surgical and endovascular care, a significant number of patients with severe PAD that undergo revascularization procedures are readmitted because of persistent symptoms and loss of patency. Restenosis occurs frequently, within the first year after an intervention. There remains an urgent need for adjunctive therapies that aid in the improvement of tissue blood flow and consequently relieve pain and improve functional capacity in these patients.

2.0 Rationale and Specific Aims

One emerging adjunctive therapy that has the potential to enhance the benefits of revascularization procedures for severe PAD is the application of intermittent pneumatic leg compressions (IPC). This is a non-invasive intervention, consisting of an air pump inside inflatable cuffs that are wrapped around the feet, ankles, and calves and worn for two hours daily. Every 20 second, the cuffs rapidly inflate, followed by rapid deflation. We and others have previously shown that exposure to IPC markedly enhances leg blood flow and vascular shear-stress in the arteries of the leg (2, 6, 7). Our preliminary work shows that 2 weeks of daily application of IPC enhances exercise tolerance in a model of PAD, in part by enhancing blood flow to collateral-dependent tissues (4). IPC has also been shown to reduce amputation rates in patients with CLI without a revascularization option. The objective of this *pilot* study is to establish evidence to support the validity of IPC in improving the outcome of lower-extremity revascularization for severe PAD. Our central hypothesis is that the treatment with IPC will lead to greater improvements in leg hemodynamics as compared to a sham device. As a result, we anticipate that patients treated with IPC will report less rest pain, have enhanced walking endurance and improved calf muscle oxygenation resulting in a subsequent improvement in quality of life. To test this hypothesis, we propose the following specific aim:

Figure 1: Intermittent pneumatic compression device

SPECIFIC AIM: Determine the effects of IPC following revascularization in patients diagnosed with severe PAD.

Patients will be enrolled in the study approximately 3 months after the revascularization procedure and will be randomly assigned to one of two groups: IPC or placebo pump. Patients will receive a commercially available IPC device (ArtAssist, ACI Medical, San Marcos, CA) and will be asked to apply the treatment to both legs at home for 2 hours daily during 3 consecutive months. Prior to the onset of the treatment and 1 and 3 months after daily home-based IPC , we will assess patient's leg hemodynamics, rest pain, calf muscle oxygenation during exercise, walking endurance and quality of life. We expect beneficial changes in leg hemodynamics, reduced rest pain, increased levels of exercise tolerance, improved calf muscle oxygenation during exercise, and improved quality of life, (QOL) as assessed by responses to VascuQol and SF36 questionnaires. The ankle-brachial index (ABI), the toe-brachial index (TBI), and rest pain will be assessed on the leg undergoing the revascularization procedure and the opposite leg. Transcutaneous PO2 (TcPO2) and calf muscle oxygenation will only be assessed in the leg undergoing revascularization.

3.0 Inclusion/Exclusion Criteria

Inclusion criteria

1) At least 18 years of age
2) Evidence of significant obstructive disease for one or multiple lower extremity arteries, as identified by prior ABI, TBI, CT angiography, ultrasound, or MR imaging
3) Completed endovascular or surgical revascularization of one or both lower extremities within the past 3 months (± 14 days)

Exclusion criteria

1) Chronic kidney disease (eGFR <30 by MDRD or Mayo or Cockcroft-Gault formula)
2) Open and/or non-healing wounds in the areas covered by the IPC cuff
3) Inability to walk on the treadmill
4) Abnormal baseline treadmill stress test
5) Walking limited by a symptom other than PAD
6) Inability to independently and correctly position the IPC cuff on legs and feet
7) Presence of any clinical condition that makes the patient unsuitable to participate in the trial
8) Concern for inability of the patient to comply with study procedures and/or follow up (e.g., alcohol or drug abuse)
9) Acute deep vein thrombosis (DVT) either suspected or diagnosed
10) Uncontrolled infection
11) Increased pain with ArtAssist device operating or with worsening skin tissue condition
12) During episodes of inflammatory phlebitis or pulmonary embolism
13) When increased venous or lymphatic return is undesirable including presumptive evidence of congestive heart failure

4.0 Enrollment/Randomization

Patients will be recruited by Dr. Raghu Motaganahalli and his associates at the Indiana University Health Methodist Hospital, Indiana University Health West Hospital and Indiana University Health Arnett. Patients that fulfill the inclusion criteria and are interested in participating in the protocol will receive detailed instructions about the experimental set-up and measurements and will be given a consent form. After providing consent, patients will be asked to complete the baseline assessment, including the assessment of leg hemodynamics, rest pain, calf muscle oxygenation during exercise, walking endurance and quality of life. Patients will be randomized into one of two groups: IPC (n=4) or placebo pump (n=4). Patients will receive an IPC device and will be asked to apply the treatment at home for 2 hours daily during 3 consecutive months. Outcomes will be reassessed 1 and 3 months after the onset of home-based treatment.

5.0 Study Procedures

After enrollment, subjects will be asked to complete two experimental sessions for baseline testing. The procedures involved in each visit are listed on Table 1. Subjects will be asked to fast overnight and refrain from smoking or using alcohol for 4 hours prior to attending all experimental sessions. Subjects will be permitted to take their usual morning medication. Although fasting and refraining from tobacco, alcohol and exercise are desired for testing consistency, it will not be considered a protocol deviation if the subject does not follow these instructions prior to one of the study visits. On **visit 1**, demographic and anthropometric characteristics from participants will be initially recorded. Patients will be asked to report the pain in their legs using visual analog scale (VAS). The study coordinator will demonstrate how to operate the IPC pump on how to wear the legs cuffs. Participants will be given the opportunity to independently place the cuffs around their legs. Individuals that are unable to successfully complete this task without help will be excluded from the study. Participants will then perform a standard symptom-limited cardiopulmonary exercise test on a treadmill. A near-infrared spectroscopy (NIRS) system, which measures skeletal muscle oxygenation, will be placed on the calf of the most symptomatic leg. Participants with an abnormal baseline treadmill stress test, including signs of coronary ischemia and an exaggerated pressor response, will be excluded from the study. This session (Visit 1) will be performed at Methodist Hospital and is expected to last approximately 3 hours.

At least 72 hrs after visit 1, subjects will be asked to return for **visit 2**. Participants will be asked to lay supine and a member of the Vascular Access Team (VAT) will draw a blood sample (20 mL) from one antecubital vein in the arm. Next, participants will undergo the bilateral assessment of the ankle-brachial index (ABI), the toe-brachial index (TBI) and transcutaneous PO2 (TcPO2) following standard of care practices. Patients will be asked to report the pain in their legs using visual analog scale (VAS). Patients will then be escorted to the exercise testing lab to undergo a graded, symptom-limited cardiopulmonary exercise test on a treadmill as described for visit 1. At the end of the session, subjects will be asked to fill out two questionnaires to assess generic (36-item Short-Form Health Survey) and disease-specific (Walking Impairment Questionnaire) quality of life. Next, patients will be trained on how to operate the IPC pump on how to wear the cuffs and will undergo a 15-min practice treatment session. At the end of the practice session, participants will be trained on: 1) how to wash and care for the inflatable cuffs, 2) how to turn the pump on and off, 3) how to record usage time on a logbook. Participants will receive the ArtAssist device (ACI Medical Inc, San Marcos, CA, USA) for IPC application. This device applies compressions to both the calf and foot, at a pressure of 120 mmHg for 3 seconds

per cycle, and this continues for three cycles per minute with a 1-second delay between different segment inflation. Patients allocated to the control group will receive a sham device, that applies a pressure of 30 mmHg at the frequency specified above. Participants on both groups will be asked to apply the cuffs to both legs and use the device while seated for 2 hours daily for 3 months. This session (Visit 2) will be performed at IU's Methodist Hospital and is expected to last approximately 4 hours.

Patients in both groups will receive weekly telephone calls from the study coordinator to verify compliance and will receive a logbook to record their sessions. A timer built into the IPC unit, and inaccessible to patients, will also provide an estimate of the patients' compliance with the treatment regimen. The logbook is intended to assist the participant keep track of the daily treatments; it will not be a protocol deviation if the logbook is not returned at the end of the treatments. Compliance with daily treatment will be formally assessed and documented with the weekly phone call from the study team. A protocol deviation will occur when either 3 consecutive home treatments are not performed or when 8 or more home treatments are not performed during the 3-month treatment period.

Outcomes will be reassessed after 1 month of treatment (end of week 4 ± 7 days) and at the completion of the intervention (end of week 12 ± 7 days). The protocol for these outcome visits will be similar to visit 2 as detailed in the table below. To ensure that the chronic rather than the acute effects of IPC are investigated, participants will be asked to interrupt the treatment 48 hrs prior to the outcome sessions. Although interrupting the treatment 48 hours prior to the outcomes sessions is desired for testing consistency it will not be a protocol deviation if a subject does not interrupt the treatment as instructed.

Visit #	Time point	Procedures
1	Baseline	Consenting Rest pain measurement Demonstration of device operation and proper cuff placement Familiarization with Cardiopulmonary Treadmill test
2	Baseline	Blood draw ABI, TBI and $TCPO_2$ Rest pain measurement Cardiopulmonary Treadmill test Quality of life questionnaires Familiarization with treatment
3	1 month	Blood draw ABI, TBI and $TCPO_2$ Rest pain measurement Cardiopulmonary Treadmill test Quality of life questionnaires
4	3 months	Blood draw ABI, TBI and $TCPO_2$ Rest pain measurement Cardiopulmonary Treadmill test Quality of life questionnaires

Table 1: Study timeline and experimental procedures that will be performed on each session

Outcome Measures:

Rest pain: Rest pain will be measured bilaterally with a 10-cm visual analog scale (VAS) at baseline and each follow-up visit. Patients will be instructed to place a mark on a line from 0 cm (no pain) to 10 cm (worst pain previously experienced) that would best describe the level of pain in the index limb during the previous 24 hours prior to examination. The distance from the 0-cm mark will then be measured and recorded.

Cardiopulmonary Treadmill Exercise Test: Participants will perform a graded, symptom-limited exercise test on a treadmill following the Gardner protocol (treadmill speed of 2 mph, 0% grade with increments of 2% every 2 min), as described previously by our group (5). During the test, the microvascular oxygenation status of the gastrocnemius muscle of the leg undergoing revascularization will be continuously monitored using a near-infrared spectrometer (NIRS) (5). Gas exchange and ventilatory variables will be measured breath-by-breath during exercise and recovery using a computer-based system (5).

Leg hemodynamics: The ankle-brachial index (ABI) and the toe-brachial index (TBI) will be measure bilaterally following standard of care practices. Transcutaneous PO2 (TcPO2) will be measured only in the leg undergoing revascularization.

Quality of life assessment: Participants will be asked to fill out the the 36-item Short-Form Health Survey and the Vascular quality of life questionnaire (VascuQoL-6) health-related quality of life questionnaires.

Biomarkers of coagulation and fibrinolysis: Blood levels of markers of coagulation and fibrinolysis will be measured in the Pathology laboratory using standard methods.

Potential risks to subjects:

Treadmill Cardiopulmonary Exercise Test: Intervention trials in PAD have demonstrated the ability of the graded treadmill exercise test to safely and robustly quantify changes associated with efficacious interventions (3). This test has been shown to be very safe, even in populations with underlying high-risk cardiovascular diagnosis (8), including patients with PAD (1). However, there is a chance that patients may experience chest pain, intolerable dyspnea, leg cramps, staggering, diaphoresis, and dizziness. The Treadmill Test will be conducted in the Heart Station where a Cardiologist is present 8AM to 5PM daily. Participants with an abnormal baseline treadmill stress test, including signs of coronary ischemia and an exaggerated pressor response, will be excluded from the study.

IPC: There are no known side effects to IPC. It has been reported that patients with severe PAD may experience pain during initial exposure to the treatment.

Venous blood sampling: During blood sampling there is a risk of pain from the needle. Bleeding, local swelling, bruising and formation of a hematoma might also occur around puncture site.

Measurement of calf muscle oxygenation: There are no risks associated with calf muscle oxygenation measurements.

Rest pain measurement: There are no risks associated with rest pain measurements.

6.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

If the patient is injured due to participation in this study, he/she will be instructed to contact the study investigators. Patients will also be advised to contact the Human Subject Office at Indiana University if they have questions about their rights while taking part in the study.

7.0 Study Withdrawal/Discontinuation

Participation in this study is voluntary. Participants may choose not to participate or, if they agree to participate, they can withdraw their participation at any time without penalty or loss of benefits to which they are otherwise entitled.

8.0 Statistical Considerations

The results obtained in this pilot experiment will allow us to demonstrate the feasibility of recruitment, randomization and intervention implementation and will provide the necessary data to support pursuit of a larger randomized clinical trial. Walking tolerance, limb hemodynamics and muscle oxygenation parameters will be compared between groups with two-way repeated-measures ANOVA, followed by Tukey's post hoc test when appropriate. We estimate that 4 subjects per group are needed to show feasibility and to provide support to our hypothesis that repeated exposure to IPC improves leg hemodynamics and reduces leg pain in patients with severe PAD recovering from peripheral revascularization.

9.0 Privacy/Confidentiality Issues

Information produced by this study will be stored in the investigator's file and identified by a code number only. The code key connecting the patient's name to specific information about the patient will be kept in a separate, secure location. Information contained in the patient's records may not be given to anyone unaffiliated with the study in a form that could identify the patient without their written consent, except as required by law.
The results of this study may be published in a medical book or journal or used for teaching purposes. However, the patients' name or other identifying information will not be used in any publication or teaching materials without their specific permission.

The patient's name and social security number will be given to the business office for facilitating payment, but will not be used for any other purposes.

10.0 Follow-up and Record Retention

Records relating to this study will be retained for at least 7 years after completion of the research. Paper records will be shredded and recycled. Records stored on a computer hard drive will be erased using commercial software applications designed to remove all data from the storage device.

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