Heat therapy for Intermittent Claudication
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Study protocol: We will conduct a randomized, controlled trial to evaluate the benefits of participating for 8 weeks in a home-based daily treatment with HT or a thermoneutral control intervention, as assessed by vascular function, walking tolerance and quality of life. The treatment duration (8 weeks) was chosen based on the recent report of Brunt and co-workers that the improvement in endothelium function promoted by repeated HT in sedentary individuals peaks at 8 weeks following the onset of treatment (Brunt et al., 2016b). Men and women with a history of stable IC and resting ankle-brachial index (ABI) of <0.9 but >0.4 in at least one leg, will be recruited to participate in this study. The exclusion criteria are: (1) uncontrolled diabetes (HbA1C > 8.5 measured within 3 months prior to date of consent), (2) heart failure, (3) chronic obstructive pulmonary disease (COPD), (4) critical limb ischemia (ischemic rest pain or ischemia-related, non-healing wounds or tissue loss, (5) prior amputation, (6) exercise-limiting comorbidity (i.e., angina, dyspnea or arthritis), (7) recent (<3 months) infrainguinal revascularization (surgery or endovascular revascularization), (8) plans to change medical therapy during the duration of the study, (9) active cancer, (10) chronic kidney disease (eGFR <30 by MDRD or Mayo or Cockcroft-Gault formula), (11) HIV positive, active HBV or HCV disease, (12) presence of any clinical condition that in the opinion of the principal investigator makes the patient not suitable to participate in the trial, (13) peripheral neuropathy, numbness, or paresthesia in the legs, (14) class 2 or 3 obesity (BMI ≥ 35 kg/m2) or unable to fit into water-circulating pants, and (15) contraindications to MRI (Levine et al., 2007). Participants will be asked to report to the laboratory for a total of 9 experimental visits throughout the study as, detailed below in Table 1. After providing written informed consent, patients will be familiarized with the treadmill cardiopulmonary exercise test and the 6-min walk test. At least 72 hrs after the familiarization visit, subjects will be asked to return for the first experimental session, during which they will undergo: (1) a resting blood draw, (2) ABI measurement, and (3) a symptom-limited, treadmill exercise test. The second experimental session will be conducted at least 48 hrs after the first session, and will encompass the following measurements: (1) calf reactive hyperemia using arterial spin labeling MRI, (2) cutaneous microvascular reactivity of the leg using a local heat challenge, (3) maximal walking distance on a 6-min walk test, and (4) QOL testing using the VascuQol and SF36 questionnaires. After baseline characteristics are established, patients will be randomized into one of two groups as detailed below. Outcomes will be reassessed at the halfway point (end of week 4), at the completion of the intervention (end of week 8) and at a follow-up visit, 4 weeks after the end of the intervention (week 12). To ensure that the chronic rather than the acute effects of HT are investigated, participants will be asked to interrupt the treatment 48 hrs prior to the outcome sessions. The primary outcome will be the change in 6-min walk distance at 4 and 8 weeks relative to baseline.

Visit #	Time point	Procedures
1	Baseline	Consenting and familiarization with treadmill test and 6-min walk test
2	Baseline	Blood draw, ABI measurement, treadmill test
3	Baseline	Calf MRI, cutaneous microvascular reactivity, QOL, 6-min walk test
4	Mid-treatment (week 4)	Blood draw, ABI measurement, treadmill test
5	Mid-treatment (week 4)	Calf MRI, cutaneous microvascular reactivity, QOL, 6-min walk test
6	End of treatment (week 8)	Blood draw, ABI measurement, treadmill test
7	End of treatment (week 8)	Calf MRI, cutaneous microvascular reactivity, QOL, 6-min walk test
8	Follow-up (week 12)	Blood draw, ABI measurement, treadmill test
9	Follow-up (week 12)	Calf MRI, cutaneous microvascular reactivity, QOL, 6-min walk test

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

Study Groups and Randomization: A total of 32 patients will be recruited by Dr. Raghu Motaganahalli from the stable vascular disease clinic at the Richard L. Roudebush VA Medical Center and at the Indiana University Methodist Hospital, as well as by the staff from the Indiana CTSI Research Networks office. After the initial outcome measurements are collected, patients will be randomized (blocked and stratified by sex), using SAS Version 9.4, into one of two groups: those receiving HT (n=16) or those receiving thermoneutral control (n=16). Patients in both groups will be provided with identical water-circulating trousers and a portable heating pump (HTP-1500, Adroit Medical Systems), and will be instructed on how to operate the equipment. The pump given to participants in the HT group will be adjusted to circulate water at 48ºC through the trousers, while the pump given to patients in the thermoneutral control group will circulate water at 33ºC to maintain skin temperature at baseline levels (Neff et al., 2016). We will ask subjects to apply the therapy daily for 90 min while seated or in

the supine position. This treatment duration was chosen based on our recent findings that leg blood flow increases progressively during exposure to HT, attaining peak levels at 80 min (Neff et al., 2016). A built-in timer inside the pumps and inaccessible to patients, will provide an estimate of patient compliance with the therapy. Patients in both groups will also receive weekly telephone calls from the study coordinator to verify compliance and will receive a logbook to record their sessions. Throughout the course of the study, daily walking will be monitored using a step activity monitor attached to the ankle of the most symptomatic leg (StepWatch3, Ortho Innovations). Participants will be asked to wear the monitor during waking hours and to remove it before sleeping and while showering. The step activity monitor continuously records the number of steps per minute and the number of minutes spent walking each day, for up to 50 days. Data will be downloaded from the monitor on week 4, on week 8 and at the follow-up visit at week 12.

Outcome Measures:

6-min Walking Test (Primary outcome): Participants will receive standardized instructions and will be asked to walk the greatest distance possible by walking back and forth along a 100-ft corridor for 6 min. We recently reported that the distance covered in 2 tests conducted 10 min apart in patients with symptomatic PAD is remarkably similar (Neff et al., 2016). This observation lends support to the concept that test-retest reliability of the 6-min walk test is excellent in this patient population (McDermott et al., 2014).

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 (Roseguini et al., 2014). During the test, the microvascular oxygenation status of the gastrocnemius muscle of the most symptomatic leg will be continuously monitored using a near-infrared spectrometer (NIRS) (Roseguini et al., 2014).

Calf Reactive Hyperemia: Peak hyperemic perfusion of the calf muscles will be assessed using pulsed arterial spin labeling (PASL) MRI (Lopez et al., 2015). MRI scans will be performed on a Siemens 3 Tesla (T) Magnetom Prisma scanner (Siemens AG Healthcare Sector, Erlangen, Germany). Subjects will have a transmit/receive knee coil placed around the most symptomatic leg. Initially, baseline perfusion images will be acquired after 30 min of rest. Next, a blood pressure cuff firmly wrapped around the lower thigh will be inflated to suprasystolic values (>75 mmHg above systolic blood pressure) for 5 min. Hyperemic flow will be measured for 5 min after cuff deflation. Regions of interest (ROIs) for each muscle group in the calf will be drawn to obtain perfusion measurements in ml/min-100 g (Lopez et al., 2015).

Cutaneous Microvascular Function: Laser-Doppler flowmetry probes, seated in the center of local skin heaters (Moor Instruments, UK), will be used to measure red blood cell flux, an index of skin blood flow (SkBF). Baseline SkBF will be recorded for 10 min, after which local skin temperature will be increased to 39°C (0.1°C/s) and maintained at this level for 40 min. Next, to induce maximal vasodilation, the local skin temperature will be elevated to 43°C. Cutaneous vascular conductance (CVC) will be calculated as laser-Doppler flux divided by mean arterial pressure (MAP), measured throughout the study via brachial artery oscillation, and normalized to maximal vasodilation (% CVCmax) (Wong and Fieger, 2010, Wong and Minson, 2011).

Quality of Life: QOL will be assessed by responses to VascuQol (Regensteiner et al., 1996) and SF36 (Ware et al., 1996) questionnaires.

Statistical Analysis and Sample Size: Baseline differences in demographics and clinical characteristics between groups will be determined using independent two-sample t-tests. Linear mixed effects models will be used to model all outcomes with baseline outcome treated as a covariate. Sex will also be included as a covariate since several outcomes are known to differ by sex (Gardner et al., 2010, Gardner et al., 2014b); however, treatment effects are not expected to differ by sex (McDermott et al., 2014) so we have not powered the study to test for sex interactions. The sample size (n=32; 16 per group) is based on the ability to detect a clinically significant change in 6-min walk distance (from baseline) over 8 weeks (primary outcome) in the HT-treated group as compared to the control group. The studies of McDermott and co-workers (McDermott et al., 2013) and Gardner and co-workers (Gardner et al., 2014a), in which the benefits of home-based exercise training on walking tolerance in patients with IC were investigated, were used as a reference for the sample size calculations. We estimated the standard deviation of change in 6-min walk distance to be 48.69 meters, based on the standard deviation of the change scores observed in Table 3 of Gardner et al (Gardner et al., 2014a). Since investigators in both studies reported a non-significant change in 6-min walk in the attention-control group [95% confidence interval for McDermott's study (health education control group, 6 month follow-up) is (-25.4 to 3.2) and for Gardner's study (light resistance training control group, 12 week follow-up) is (-6.33 to 14.33)], we hypothesize that the change in 6-min walk in the control group in our study will be non-significant (0 on average). As pointed

out by Perera et al (Perera et al., 2006), a change of 50 meters in the 6-min walk test is considered substantial and clinically meaningful in elderly subjects. Using this effect size ((50-0)/48.42=1.03), we determined that 16 subjects per group will be needed to detect a clinically meaningful improvement by HT therapy, with a power of 80% and based on a two-sided, two-sample t-test with significance level 0.05. Power will be improved through our linear mixed models approach. Based on our expected enrollment rate of 2 patients/month, we will be able to complete accrual in 16 months.

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