Published in final edited form as:

Nurs Res. 2017 ; 66(5): 378–387. doi:10.1097/NNR.0000000000000230.

The Relationship Between Peripheral Artery Disease (PAD) Symptomatology and Ischemia

Erica N. Schorr, PhD, RN [Assistant Professor],

School of Nursing, University of Minnesota, Minneapolis, MN

Diane Treat-Jacobson, PhD, RN, FAAN [Associate Professor], and

School of Nursing, University of Minnesota, Minneapolis, MN

Ruth Lindquist, PhD, RN, ACNS-BC, FAAN

Professor, School of Nursing, University of Minnesota, Minneapolis, MN

Abstract

Background—Fewer than half of individuals with peripheral artery disease (PAD) experience classic claudication and the relationships between PAD typical or atypical symptom intensity, location, and description (classic or atypical) with ischemic changes have not previously been reported.

Objective—The primary purpose of this study was to evaluate the relationship between self-reported PAD symptom intensity and calf tissue ischemia measured using the tissue saturation index (TSI) during treadmill exercise. The location and descriptors of atypical PAD symptoms in the presence of calf tissue ischemia were also identified.

Methods—Adults with PAD with exercise-limiting ischemic symptoms were asked to: (a) rate symptom intensity using a numerical rating scale (NRS) from 0 to 5 (0 = *no pain*, 1 = *onset of pain*, 5 = *maximal pain*); (b) provide symptom locations and descriptors; and (c) wear a near-infrared spectroscopy device to obtain calf TSI values during treadmill exercise. Multilevel models with TSI as the outcome variable were estimated during exercise and recovery. Covariates included were: exercise time, recovery time, baseline TSI, exercise rating, recovery rating, ABI, age, race, sex, BMI, diabetes, neuropathy, and smoking.

Results—During three successive bouts of treadmill exercise for 40 participants (80% Caucasian males; average age 68 years, $SD = 9.2$), the most rapid decline in TSI occurred between the start of exercise and symptom onset (NRS = 1). The TSI nadir was often reached prior to report of maximum discomfort (NRS = 5) and changes in TSI were related to exercise time ($p < .001$), baseline TSI ($p < .001$), exercise ratings ($p < .001$), and ABI ($p < .05$). During recovery, TSI increased steadily for most participants as pain eased. In the recovery model, changes in TSI were associated with recovery ratings ($p < .001$) and ABI ($p < .03$). Out of 120 treadmill exercise tests, 69.2% were stopped due to discomfort in the calf with classic descriptors reported only half the time (55.4%).

Corresponding Author: Erica Schorr, University of Minnesota School of Nursing, 5-140 WDH, 308 Harvard St. SE, Minneapolis, MN 55455 (e-mail: scho0828@umn.edu).

The authors have no conflicts of interest to report.

Discussion—Exploratory analyses revealed ischemic symptoms extended beyond classic claudication locations and descriptors. Future research should evaluate changes in TSI relative to atypical locations and descriptors to improve understanding of the full range of ischemic symptoms experienced by individuals with PAD.

Keywords

claudication; exercise; infrared spectroscopy; peripheral vascular disease; treadmill test

Peripheral artery disease (PAD) is a progressive atherosclerotic occlusive disease affecting more than 8 million Americans and over 200 million individuals worldwide; sharp rises are expected due to population aging (Allison et al., 2007; Fowkes et al., 2013; Ostchega, Paulose-Ram, Dillon, Gu, & Hughes, 2007). PAD is an independent risk factor for cardiovascular events and mortality; therefore, early detection and treatment are crucial to potentially prevent heart attack, stroke, and death (Criqui & Aboyans, 2015; Criqui, Ninomiya, Wingard, Ji, & Fronek, 2008; Diehm et al., 2009; Leng et al., 1996). In PAD, arterial blood flow to the lower extremities is reduced, leading to exertional skeletal muscle ischemia that results in significant discomfort—even while walking short distances (Falcone et al., 2003). The discomfort typically commences shortly after walking begins and resolves only when the activity ceases. Classic claudication is the most commonly recognized symptom of PAD and is described as an aching, cramping, and painful or tired feeling in the calves (Rose, 1962).

The presentation and progression of PAD symptoms varies and may differ based on disease severity, disease location, age, the presence of certain comorbid conditions, such as neuropathy, arthritis, and spinal stenosis (McDermott et al., 2001; Newman et al., 2001), or other unidentified factors. It is suspected that there are age- and gender-specific PAD symptoms beyond those of classic claudication; however, any such symptoms remain unconfirmed since the relationship between symptom reporting (intensity, location, and description), and changes in lower extremity tissue oxygenation during exercise is unknown (Schorr & Treat-Jacobson, 2013; Stoffers et al., 1996).

Although classic claudication is considered the hallmark symptom of PAD, only 7.5% to 33% of individuals with PAD report classic claudication as being part of their symptom experience (Schorr & Treat-Jacobson, 2013). Since many patients with PAD do not experience classic claudication, heavy reliance on this symptom for screening and detection can result in mis- or underdiagnosis of the disease; thus, significant cardiovascular comorbidities and the incidence of mortality may increase (Criqui, Fronek, Klauber, Barrett-Connor, & Gabriel, 1985; McDermott, Mehta, & Greenland, 1999; Stoffers, Rinkens, Kester, Kaiser, & Knottnerus, 1996). For example, an individual reporting symptoms that are inconsistent with classic claudication may not trigger provider suspicion of the presence of PAD; therefore, individuals may not receive the necessary diagnostic testing and subsequent treatment for this chronic, debilitating disease.

PAD symptom reporting generally includes a verbal report of symptoms to a healthcare provider and written completion of a PAD symptom questionnaire in a static condition (e.g., questions about symptoms are answered during an office visit rather than during exercise

when ischemia is actively occurring). Since exercise increases oxygen demand, it can be used to provoke PAD symptoms, enabling symptom assessment using a numerical rating scale (NRS) to capture the onset and progression in symptom intensity. To date, researchers have collected data on symptom rating (Treat-Jacobson, Henly, Bronas, Leon, & Henly, 2011) and perceived exertion during graded treadmill exercise (Collins et al., 2012)—in some cases, simultaneously measuring changes in tissue saturation index (TSI) (Miranda et al., 2012). However, analyzing TSI changes in relationship to symptom intensity or perceived exertion data is lacking. To our knowledge, this study is the first of its kind to collect data on self-reported symptoms of ischemia during exercise and recovery and, subsequently, evaluate the relationship between changes in calf tissue oxygenation (using TSI) and self-reported symptom intensity during treadmill exercise and recovery. Data on symptom intensity, location, and descriptor enabled a preliminary differentiation of symptoms related to ischemia versus nonischemic symptoms during three phases: at rest, during exercise, and during recovery, based on a previously published conceptual model of symptom differentiation (Schorr & Treat-Jacobson, 2013). For example, heel discomfort at a constant intensity during exercise or sustained quadriceps discomfort would be considered nonischemic symptoms since symptoms consistent with ischemia are progressive in nature and consistently relieved during recovery. This was a necessary first step toward the creation of a more comprehensive set of diagnostic PAD symptom descriptors, including atypical symptoms, as well as symptom descriptors manifesting comorbid conditions unrelated to PAD (i.e., symptom confounders) (Schorr & Treat-Jacobson, 2013). This preliminary work laid a foundation for work toward the long-term goal of developing and refining age- and gender-specific PAD screening tools to improve and increase lifesaving detection, diagnosis, and treatment.

Purpose

The purpose of this study was to: (a) evaluate the relationship between PAD symptom intensity and changes in calf tissue ischemia during treadmill exercise and recovery; and (b) explore symptom locations and descriptors atypical of PAD reported in the presence of calf tissue ischemia.

Methods

Design

This was a descriptive, exploratory study that examined the symptoms experienced by individuals with PAD during treadmill exercise and recovery (active and static conditions). In addition to completing the treadmill testing, participants were interviewed about their symptom experiences (see Schorr, Peden-McAlpine, Treat-Jacobson, & Lindquist, 2015). During treadmill testing, calf tissue oxygenation via near-infrared spectroscopy (NIRS) and patient report of symptom intensity were obtained simultaneously. All protocols were reviewed and approved by the Institutional Review Board at the University of Minnesota.

Sample

Inclusion criteria were: (a) an ankle-brachial index [ABI] ≥ 0.90 or a post-exercise drop in ABI confirming PAD), (b) exercise-limiting claudication or ischemia-related symptoms, (c) deemed safe to exercise based on the results of a cardiac stress test within the last 12 months, (d) English-speaking, (e) aged 21 years or older, and (f) able to provide informed consent. Individuals were excluded from participation if they had (a) uncontrolled hypertension (systolic blood pressure >200 mmHg and/or diastolic blood pressure >100 mmHg), (b) a vascular procedure within the last three months, or (c) exercise capacity limited by health problems other than claudication, such as angina or extreme dyspnea on exertion.

All study participants were recruited from the **EXercise Training to Reduce Claudication: Arm ERgometry versus Treadmill Walking (EXERT)** study which used the same inclusion and exclusion criteria listed previously (Treat-Jacobson, Bronas, & Leon, 2009). This study examined the efficacy of two forms of supervised exercise, arm ergometry and treadmill walking, compared to usual care provided by a physician for the treatment of PAD. All past or current EXERT participants assigned to any of the three EXERT treatment groups were eligible for participation. Previous EXERT participants received a letter describing the ancillary study, and current participants received a verbal description of the ancillary study by EXERT study staff. All current EXERT participants who were approached agreed to be contacted for potential participation in this ancillary study. The figure in Supplemental Digital Content 1 provides the details of study recruitment and enrollment ($N = 40$).

Measures

Demographic and clinical information—Data obtained from the medical record included primary medical diagnosis, comorbid conditions, previous procedures and outcomes related to exercise and PAD, previous ABI values, cardiac stress test results, and medications. Additional data, including age, gender, education, ethnicity, and employment, were collected with a standard demographic form.

Ankle-brachial index (ABI)—The ABI, the ratio of ankle to arm systolic blood pressure (BP), was used to confirm the presence of PAD and to determine disease severity at the time of study enrollment. Participants rested for 10 minutes in the supine position, relaxed, head and heels supported, in a room with comfortable temperature prior to using a blood pressure cuff, a standard sphygmomanometer, and a Doppler probe to obtain bilateral arm and leg systolic pressures according to standard procedures (Aboyans et al., 2012; Grenon, Gagnon, & Hsiang, 2009). An ABI ≥ 0.90 or a postexercise drop in ABI is diagnostic of PAD (Aboyans et al., 2012). ABI was treated as a categorical variable, using five categories of PAD severity: < 0.50 (severe PAD), 0.50 to less than 0.70 (moderate PAD), 0.70 – 0.90 (mild PAD), 0.91 – 0.99 (borderline PAD), and >1.40 (non-compressible arteries indicating PAD).

Subjective symptom reporting—Symptom data included the intensity rating, location, and descriptor for each symptom experienced by participants during exercise and recovery. Symptom intensity was measured at the onset of symptoms and throughout symptom progression using a 6-point numerical rating scale (NRS). A scale ranging from 0 = *no*

discomfort, 1 = *symptom onset*, and 5 = *maximum discomfort experienced*. During recovery, a rating of 0 corresponded to complete cessation of symptoms. Participants were encouraged to report symptoms they thought were related to PAD, as well as those presumed to be unassociated with the disease.

Objective measurement of calf tissue oxygenation—Calf tissue oxygenation was measured using near-infrared spectroscopy (NIRS). The Artinis Medical Systems B.V., PortaMon NIRS device provided baseline and continuous-wave measurement of tissue oxygenation, reported as Tissue Saturation Index (TSI) and expressed as a percentage, in the exercising calf muscle to determine the degree of calf tissue ischemia during static and active conditions (i.e., recovery and exercise). The PortaMon NIRS generated near-infrared light at two wavelengths, 760 nanometers (nm) and 850 nm, from three light emitting diodes (interoptode distances of 30, 35, and 40 mm between the receiver and each of the three diodes). NIRS has been shown to be an inexpensive, noninvasive, accurate, stable, and sensitive tool to study the interactions between oxygen delivery and utilization in human skeletal muscle (Wariar, Gaffke, Haller, & Bertocci, 2000). Among individuals with PAD, NIRS has demonstrated moderate-to-high test-retest reliability (Miranda et al., 2010; Miranda et al., 2012); parameters measured with NIRS can establish PAD presence, severity, and response to treatment, and correlate well with ABI (Ferrari, Mottola, & Quaresima, 2004; Manfredini et al., 2009; Vardi & Nini, 2008).

Study Procedures

After participants provided informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization, data were collected from each participant's medical record.

Treadmill familiarization and testing—Treadmill familiarization was completed prior to exercise testing to ensure participant safety and adequate understanding of treadmill exercise testing procedures, and to determine the appropriate speed and grade for individual exercise testing. The speed during treadmill familiarization began at 1.5 miles per hour (mph) at a 0% grade. Both speed and grade were adjusted as necessary to induce ischemia-related discomfort within 3 minutes of commencing treadmill walking. The starting speed and grade for treadmill testing was individualized and determined by the results of the treadmill familiarization. Speed and grade progression were also individualized to prevent high-functioning participants from stopping the test due to symptoms other than calf ischemia and to prevent provoking discomfort too early in more severely limited participants, which would have potentially condensed symptom reporting. The average starting speed and grade was 2 mph at a 0% grade, with an increase in grade to 2% at 2 minutes. Thereafter, grade was increased by 1% every two minutes, maintaining a speed of 2 mph. If participants continued walking, the speed was increased to 2.5 mph at 16 minutes.

Next, participants verified their medical records and provided demographic information. After resting quietly in a supine position for 10 minutes, the principal investigator (PI) obtained the ABI according to standard procedures (Grenon, Gagnon, & Hsiang, 2009). The Polar heart rate (HR) monitor was placed around the participant's chest and a baseline HR

was obtained. The PortaMon NIRS was wrapped in clear cellophane and placed at the level of the largest circumference of the medial gastrocnemius muscle of the more symptomatic leg as reported by each study participant, regardless of disease severity based on the ABI. If participants reported equal symptom severity in both legs, the device was placed on the leg with the higher disease severity (i.e., lower ABI determined by confirmatory ABI). The PortaMon NIRS was covered with a black cloth, secured with Coban self-adherent wrap, and paired via Bluetooth with the dedicated study laptop computer. Equilibration as well as baseline and continuous measurements were obtained following methods consistent with previous studies (Gardner et al., 2009; Hamaoka, McCully, Quaresima, Yamamoto, & Chance, 2007; Manfredini et al., 2009; Van Beekvelt, Colier, Wevers, & Van Engelen, 2001), and the PI's previously conducted feasibility evaluation. Participants remained in a seated position while baseline HR, BP, and TSI values were obtained.

Safety measures

Exercise testing carries a small risk of heart attack (3.58 in 10,000) or death (0.50 in 10,000) (Stuart & Ellestad, 1980). Other potential risks to participants included exercise related risks such as a change in BP, HR, and/or heart rhythm. The likelihood of potential risks was believed to be minimal. The following procedures were in place to decrease the potential risks described: pre- and post-exercise BP; periodic BP during exercise; continuous HR using a PolarHR monitor strap (cutoff was 85% maximal HR based on stress test results); and pre- and post-exercise blood glucose levels for any participant with a confirmed diagnosis of diabetes mellitus (type 1 or type 2).

Each treadmill test was started at the speed and grade determined during the treadmill familiarization. Participants were asked to describe the symptom experience by providing the symptom intensity using the NRS, symptom location, and a descriptor for each location (e.g., "1/5, left calf, ache"); thereafter they were asked to report the progression of symptom intensity in whole integers on the NRS, until the maximum discomfort level was achieved (i.e., reported NRS score was 5/5). Symptom data were recorded on a paper data collection form, as well as audio-recorded for the purposes of data verification. After reaching an NRS rating of 5, the treadmill speed and grade were reduced slowly until the participant was able to safely stop walking on the treadmill. Participants were then assisted off of the treadmill and into a seated, resting position in a chair.

At the beginning of the recovery period, postexercise HR and BP were obtained. Data collection continued throughout recovery (i.e., symptom intensity, location, descriptor, and TSI values). Full recovery was reached when participants reported an NRS rating of 0 (no pain), and HR and BP returned to or fell below baseline values. Two additional exercise tests were performed during the same session, following the same procedures as the first treadmill test.

Statistical Analysis

Data were collected during the resting, exercise, and recovery phases of three consecutive treadmill tests with variable rest periods in between based on time to return to baseline

values. Statistical analysis included descriptive statistics, and multilevel modeling (MLM) (R version 3.2.2).

Multilevel model for change—Building a multilevel model allowed for an examination of the associations between self-reported symptom intensity and changes in TSI, while accommodating within-subject clustering. Multilevel modeling characterized change within and between individuals over time (Singer & Willett, 2003).

Data were organized in a person-level dataset and structured hierarchically; repeated observations were nested within individuals. The outcome variable was TSI, expressed as a percentage and recorded continuously over time. TSI values that matched up with precise time points of each symptom rating during exercise and recovery were extracted and served as the outcome variable for all models. Individual-level predictors in both the exercise and recovery conditional growth models were: baseline TSI, disease severity as measured by ABI, age, body mass index (BMI), gender, race, smoking status, diabetes, and neuropathy. Exercise time and exercise NRS ratings were included in the exercise model, whereas recovery time and recovery NRS ratings were included in the recovery model.

Multilevel modeling was divided into two phases: exercise and recovery. We accommodated intrasubject dependence by including per-subject random intercepts in the models. The estimation method was restricted maximum likelihood, which accommodates data missing at random. A likelihood ratio test determined that the random effects were necessary. There was no evidence to suggest that per-person slopes were appropriate. Individual growth curves during the exercise phase for a random subset of 12 study participants were examined and a negative, linear relationship with varying intercepts was observed. Similarly, graphical analysis of the recovery data for another random subset of 12 study participants revealed a positive and linear relationship throughout recovery. Thus, a linear growth model was selected for both the exercise and recovery phases.

Two commonly used penalized likelihood criteria served as the foundation for model selection: Akaike's information criterion (AIC) and Bayesian information criterion (BIC). Ideally, the final model would be favored by both criteria. However, BIC penalizes model complexity more heavily, so when the AIC and BIC disagreed, more consideration was given to the model favored by BIC to improve generalizability (Dziak, Coffman, Lanza, & Li, 2012; Raftery, 1995). Other model selection criteria included residual analysis and ease of interpretability. For each phase, an unconditional means model, an unconditional growth model, and a conditional model including all 11 of the predictor variables were constructed. Nominal p -values of .05 were used.

Exploratory analysis—Individual graphs of TSI, symptom intensity, symptom locations, and symptom descriptors were explored. The primary purpose was to identify atypical symptom locations and descriptors that corresponded to changes in TSI indicative of the onset, progression, and resolution of ischemia. These graphs provide insights on how to proceed with future studies that are adequately powered to identify and compare patterns of calf tissue oxygenation in the presence of atypical versus classical PAD symptom reporting.

Results

Sample

Characteristics of the 40 study participants appear in Table 1. The average age of participants was 68 years ($SD = 9.2$), more than three quarters were male (88%), predominantly Caucasian (90%), and highly educated with most having completed some college or graduate school (78%). The average ABI indicated mild disease severity ($M = 0.81$, $SD = 0.27$). However, a mode ABI between 0.50 and 0.69 indicated that the largest percentage of participants had a moderate level of disease. The majority of participants were overweight or obese with a history of smoking. The most frequently diagnosed comorbidities were hypertension and hyperlipidemia; both are risk factors for the development of PAD. The majority of study participants were taking medications to control these conditions: nearly 83% ($n = 33$) taking a cholesterol-lowering medication and an antiplatelet agent, and 70% ($n = 28$) were taking a cholesterol-lowering medication, antiplatelet agent, and antihypertensive medication.

Treadmill Exercise and Recovery

Exercise treadmill testing protocols were individualized since they were based on the results of individual treadmill familiarizations. However, the majority of participants ($n = 31$; 78%) started walking at 2 mph and 0% grade. A summary of the treadmill speed and grade, as well as the performance during the exercise and recovery phases is presented in the Supplemental Digital Content 2. On average, at each exercise test, participants walked 10 minutes and 44 seconds ($SD = 4$ minutes and 48 seconds). The average time to fully recover from exercise-induced ischemic symptoms between exercise tests was 6 minutes and 4 seconds ($SD = 4$ minutes and 10 seconds).

Ischemic Changes

Calf muscle tissue oxygenation, as measured by TSI values obtained via PortaMonNIRS, was recorded prior to the start of each test, and throughout the exercise and recovery phases. A summary of TSI values obtained during all three phases is presented in the table in Supplemental Digital Content 3. As expected, the average TSI of participants at baseline was higher than the average TSI during both the exercise and recovery phases. However, a surprising finding was that the average TSI at the point of self-reported full recovery (i.e., NRS = 0) was actually higher than the baseline average.

There was minimal intraindividual variability between exercise TSI values for each of the three treadmill tests. Similarly, variability in intraindividual TSI values was minimal across each of the three recovery phases. These data suggest individuals reached full recovery from ischemia between tests and performed consistently on all three treadmill tests (i.e., exercise duration), which eliminated the need to control for the sequence of exercise tests in multilevel modeling, simplifying the interpretation of the final model results.

Multilevel Modeling

Complete computer output for the unconditional means model, unconditional growth model, and a conditional model including all 11 of the predictor variables during exercise and recovery are available as Supplemental Digital Content 4.

Exercise—For the exercise data, 65% of the variation in TSI was attributable to individual differences ($\rho = .65$). Compared to the full model, the final model had a 14-point decrease in BIC, which provided very strong evidence to support choosing it as the final model (Dziak et al., 2012; Raftery, 1995). The final model included exercise time, baseline TSI, NRS exercise rating, ABI category, and BMI category as covariates (Table 2). Intercepts were allowed to vary by individual, but the slope was held constant. The final exercise model revealed a significant grand mean intercept and significant intercepts for each exercise rating ($p < .001$). Only three ABI categories were significantly predictive of TSI during exercise, suggesting that only moderate and severe PAD (ABI 0.50–0.69 and ABI 0.49), or noncompressible arteries (ABI >1.40), influence TSI variability during exercise.

Recovery—In the unconditional means model, within-person variation ($\sigma_e^2 = 89.41$) was smaller than the between-person variation ($\sigma_0^2 = 170.70$) and 66% of the variation in TSI was attributable to differences between individuals ($\rho = .66$). The final recovery model (Table 2) illustrated a significant grand mean intercept and significant intercepts for each recovery rating ($p < .001$). Other significant covariates included both interactions, and ABI's indicative of noncompressible arteries (ABI > 1.40) and the presence of moderate and severe disease (ABI from 0.50–0.69 and ABI 0.49). Even though none of the BMI categories were significant, BMI was included in the final model for two reasons. First, it improved the overall fit of the final model. Second, BMI explained variation in the final model that wasn't being explained by the other covariates, as evidenced by a change in the p -value of the underweight category. Comparing the BIC of the full and final models, there was a 6-point decrease. The decrease in BIC provided positive to strong evidence of choosing the final model over the full model.

Exploratory Analysis

Participants provided classic and atypical locations and descriptors during the onset, progression, and resolution of calf tissue ischemia. Some individuals described classic claudication (ache, cramp, pain, or tired in the calf) at the onset of ischemia and at the point of maximum discomfort (Figure 1, Panel A). Others reported discomfort in the classic location (calf), but used atypical words to describe ischemic changes, such as *burn*, *tight*, or *pressure* (Figure 1, Panel B). Perhaps the most interesting findings were the ischemic changes taking place while individuals reported discomfort in atypical locations using descriptors atypical of claudication. For example, a burning sensation in the foot reported at the onset of ischemia, and full symptom recovery reported when ischemia started to lessen, rather than when TSI values returned to baseline (Figure 1, Panel C). All of the symptom location and descriptor combinations provided by all 40 participants during 120 treadmill exercise tests is summarized in Supplemental Digital Content 5.

Compared to other studies reporting 100% of treadmill tests being stopped due to classic claudication (Gardner, Montgomery, & Afaq, 2007; Gardner et al., 2012), only 69.2% ($n = 83$) of exercise tests were stopped due to discomfort in the calf—the classic location, with NRS equal to 5/5 in the calf—and classic descriptors were used only half the time to describe maximum calf discomfort (55.4%, $n = 46$). All of the symptom descriptors and locations provided during exercise appear in Table 3. *Tight* was the most common atypical descriptor participants used to describe maximum calf discomfort (i.e., NRS 5/5 in the calf); Table 4 provides a list of all the calf descriptors reported. Atypical symptom-limiting locations included the hip, hamstring, foot, and heel, with participants reporting classic and atypical descriptors at the point of maximum discomfort (NRS rating of 5 out of 5) during exercise. The frequencies for all of the other lower extremity locations and descriptors reported at maximum discomfort appear in Supplemental Digital Content 6.

Discussion

The most notable findings from this study are in regards to the relationship between symptom intensity and TSI values during exercise and recovery. All of the symptom intensity categories were significant for the exercise and recovery models. During exercise, the most severe decline in TSI was observed between the start of exercise and the onset of discomfort (i.e., NRS 1/5). For most individuals, TSI continued to decline slightly throughout the duration of exercise until the maximum discomfort was reached (i.e., NRS 5/5). The stamina exhibited by some individuals was in direct contrast to those who had to stop exercising as soon as TSI declined to a specific point. It is unknown whether there was a specific compensatory mechanism that allowed some individuals to continue exercising despite low TSI values, or that enabled TSI values to increase above the minimum TSI obtained despite the progression of exercise intensity and duration.

During recovery, TSI values were at their lowest point when most participants were still experiencing maximum discomfort (i.e., NRS 5/5) and then TSI values steadily increased until full recovery was achieved (i.e., NRS 0/5). It has yet to be determined whether some individuals recover more quickly than others based on specific characteristics, such as gender or age, and why some individuals report a full recovery as soon as TSI peaks, while others don't report a full recovery until sometime after the peak TSI has been reached and, in some cases, has declined. On average, TSI values were at the highest in the immediate postexercise period, indicating a postexercise increase in calf tissue oxygenation. This finding supports the positive effects observed when individuals with PAD participate in exercise therapy and achieve improvements in walking duration and/or distance.

In both the exercise and recovery models, age was a nonsignificant predictor of TSI. These findings are consistent with existing literature supporting that age in healthy individuals has no effect on tissue saturation values (Miranda et al., 2010). Gender was also a nonsignificant predictor of TSI. Overall, male participants walked longer, but they exhibited lower TSI values. This directly contrasts the tissue saturation patterns identified in healthy subjects based on gender in which women had a 15% lower baseline TSI compared to men, with women maintaining lower values throughout exercise compared to males (Miranda et al., 2010). However, in the Miranda et al. study (2010), calf skinfold was 107% higher in

women compared to men, and calf skin temperature of women was 3% lower. Adipose tissue thickness has been identified as a factor that influences oxygenation values (Van Beekvelt, Borghuis, Van Engelen, Wevers, & Colier, 2001), while the role of skin temperature is less understood. Gender may also influence PAD symptom location and descriptor reporting, with women reporting different symptoms since symptom definitions were based on male experiences and established at a time when ischemic atherosclerotic diseases were thought to primarily affect men.

Limitations

The PortaMon NIRS could not account for factors such as collaterals, cardiac function, inotropic and chronotropic response to therapeutic agents, vessel wall stiffness, and the presence of comorbid conditions that could have influenced calf tissue oxygenation during exercise (Manfredini et al., 2009). Additionally, calf adipose tissue thickness and skin temperature were not measured in this study. Significant variations in either measure could have influenced oxygenations values. Individualized testing protocols were used to guide individuals through symptom progression, while attempting to avoid stopping exercise for any other reasons (e.g., shortness of breath or overall fatigue). But the lack of a standardized exercise testing protocol may limit the comparison of study findings with future research studies.

The sample in this study was small and relatively homogenous, and recruited from a single-parent study in one geographical location. The lack of heterogeneity could have impacted the ability to construct stronger, more accurate models, which limits generalizability of the study findings to other individuals with PAD. However, the primary purpose of this study was to summarize the data of the study sample, gain an initial understanding of the relationship between symptom intensity and calf tissue oxygenation during exercise and recovery, and identify similarities and differences in symptom reporting, including atypical locations and descriptors. Future research collecting data from a larger number of individuals in a variety of geographical locations with more diverse backgrounds and a spectrum of disease severity will strengthen generalizability of study findings.

Conclusions

Participants with PAD provided classic and atypical symptom locations and descriptors during the onset, progression, and resolution of calf tissue ischemia during and after treadmill testing. Perception of maximum discomfort frequently occurred after the TSI nadir. Similarly, most reports of full symptom recovery occurred prior to complete resolution of ischemia. The results of this research are foundational for future studies to determine patterns of calf tissue oxygenation, its relationship to symptom intensity, location and description, and potential changes with therapeutic interventions. Further research is necessary to provide more information about the characteristics of individuals reporting atypical symptoms, and to explore mechanisms that could explain the objective-subjective mismatch of all individuals with PAD—which would help better understand the full range of ischemic symptoms associated with PAD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the National Institute of Nursing Research (F31 NR012866-01), the Jonas Center for Nursing Excellence and John A. Hartford Foundation Scholar Award Program, the National Center for Research Resources (1UL1RR033183-01), and the National Center for Advancing Translational Sciences of the National Institutes of Health to the University of Minnesota Clinical and Translational Science Institute (8UL1TR000114-02).

References

- Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, Treat-Jacobson D. Measurement and interpretation of the ankle-brachial index: A scientific statement from the American Heart Association. *Circulation*. 2012; 126:2890–2909. DOI: 10.1161/CIR.0b013e318276fbcf [PubMed: 23159553]
- Allison MA, Ho E, Denenberg JO, Langer RD, Newman AB, Fabsitz RR, Criqui MH. Ethnic-specific prevalence of peripheral arterial disease in the United States. *American Journal of Preventive Medicine*. 2007; 32:328–333. DOI: 10.1016/j.amepre.2006.12.010 [PubMed: 17383564]
- Arder CI, Janssen I, Ross R, Katzmarzyk PT. Development of health-related waist circumference thresholds within BMI categories. *Obesity Research*. 2004; 12:1094–1103. DOI: 10.1038/oby.2004.137 [PubMed: 15292473]
- Collins EG, O'Connell S, McBurney C, Jelinek C, Butler J, Reda D, Grabiner M. Comparison of walking with poles and traditional walking for peripheral arterial disease rehabilitation. *Journal of Cardiopulmonary Rehabilitation & Prevention*. 2012; 32:210–218. DOI: 10.1097/HCR.0b013e31825828f4 [PubMed: 22595894]
- Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. *Circulation Research*. 2015; 116:1509–1526. DOI: 10.1161/CIRCRESAHA.116.303849 [PubMed: 25908725]
- Criqui MH, Fronek A, Klauber MR, Barrett-Connor E, Gabriel S. The sensitivity, specificity, and predictive value of traditional clinical evaluation of peripheral arterial disease: Results from noninvasive testing in a defined population. *Circulation*. 1985; 71:516–522. DOI: 10.1161/01.CIR.71.3.516 [PubMed: 3156007]
- Criqui MH, Ninomiya JK, Wingard DL, Ji M, Fronek A. Progression of peripheral arterial disease predicts cardiovascular disease morbidity and mortality. *Journal of the American College of Cardiology*. 2008; 52:1736–1742. DOI: 10.1016/j.jacc.2008.07.060 [PubMed: 19007695]
- Diehm C, Allenberg JR, Pittrow D, Mahn M, Tepohl G, Haberl RL, Trampisch HJ. Mortality and vascular morbidity in older adults with asymptomatic versus symptomatic peripheral artery disease. *Circulation*. 2009; 120:2053–2061. DOI: 10.1161/CIRCULATIONAHA.109.865600 [PubMed: 19901192]
- Dziak, JJ., Coffman, DL., Lanza, ST., Li, R. Sensitivity and specificity of information criteria. University Park, PA: The Methodology Center, The Pennsylvania State University; 2012. Methodology Center Technical Report 12-119Retrieved from <https://scholarsphere.psu.edu/collections/5712mq773>
- Falcone RA, Hirsch AT, Regensteiner JG, Treat-Jacobson D, Williams MA, Hiatt WR, Stewart KJ. Peripheral arterial disease rehabilitation: A review. *Journal of Cardiopulmonary Rehabilitation and Prevention*. 2003; 23:170–175.
- Ferrari M, Mottola L, Quaresima V. Principles, techniques, and limitations of near infrared spectroscopy. *Canadian Journal of Applied Physiology*. 2004; 29:463–487. DOI: 10.1139/h04-031 [PubMed: 15328595]
- Fowkes FGR, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, Criqui MH. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: A systematic review and analysis. *Lancet*. 2013; 382:1329–1340. DOI: 10.1016/S0140-6736(13)61249-0 [PubMed: 23915883]

- Gardner AW, Montgomery PS, Afaq A. Exercise performance in patients with peripheral arterial disease who have different types of exertional leg pain. *Journal of Vascular Surgery*. 2007; 46:79–86. DOI: 10.1016/j.jvs.2007.02.037 [PubMed: 17540534]
- Gardner AW, Parker DE, Montgomery PS, Blevins SM, Nael R, Afaq A. Sex differences in calf muscle hemoglobin oxygen saturation in patients with intermittent claudication. *Journal of Vascular Surgery*. 2009; 50:77–82. DOI: 10.1016/j.jvs.2008.12.065 [PubMed: 19223136]
- Gardner AW, Parker DE, Montgomery PS, Khurana A, Ritti-Dias RM, Blevins SM. Calf muscle hemoglobin oxygen saturation in patients with peripheral artery disease who have different types of exertional leg pain. *Journal of Vascular Surgery*. 2012; 55:1654–1661. DOI: 10.1016/j.jvs.2011.12.060 [PubMed: 22341835]
- Grenon SM, Gagnon J, Hsiang Y. Ankle–brachial index for assessment of peripheral arterial disease. *New England Journal of Medicine*. 2009; 361:e40.doi: 10.1056/NEJMc0807012 [PubMed: 19890121]
- Hamaoka T, McCully KK, Quaresima V, Yamamoto K, Chance B. Near-infrared spectroscopy/imaging for monitoring muscle oxygenation and oxidative metabolism in healthy and diseased humans. *Journal of Biomedical Optics*. 2007; 12:062105.doi: 10.1117/1.2805437 [PubMed: 18163808]
- Leng GC, Fowkes FG, Lee AJ, Dunbar J, Housley E, Ruckley CV. Use of ankle brachial pressure index to predict cardiovascular events and death: A cohort study. *BMJ*. 1996; 313:1440.doi: 10.1136/bmj.313.7070.1440 [PubMed: 8973232]
- Manfredini F, Malagoni AM, Felisatti M, Mandini S, Mascoli F, Manfredini R, Zamboni P. A dynamic objective evaluation of peripheral arterial disease by near-infrared spectroscopy. *European Journal of Vascular and Endovascular Surgery*. 2009; 38:441–448. DOI: 10.1016/j.ejvs.2009.06.011 [PubMed: 19625198]
- McDermott MM, Greenland P, Liu K, Guralnik JM, Criqui MH, Dolan NC, Sharma L. Leg symptoms in peripheral arterial disease: Associated clinical characteristics and functional impairment. *JAMA*. 2001; 286:1599–1606. DOI: 10.1001/jama.286.13.1599 [PubMed: 11585483]
- McDermott MM, Mehta S, Greenland P. Exertional leg symptoms other than intermittent claudication are common in peripheral arterial disease. *Archives of Internal Medicine*. 1999; 159:387–392. DOI: 10.1001/archinte.159.4.387 [PubMed: 10030313]
- Miranda A, Figoni SF, Castellano V, Hymans D, Kerendian N, Nguyen TT, Scremin OU. Calf muscle oxygenation during exercise in healthy adults. *Clinical Kinesiology*. 2010; 64:8–16.
- Miranda A, Figoni SF, Cha T, Flanagan T, Mandal O, Silva M, Scremin OU. Calf tissue oxygenation during exercise in men with and without risk factors for developing peripheral arterial disease. *American Journal of Physical Medicine & Rehabilitation*. 2012; 91:200–210. DOI: 10.1097/PHM.0b013e3182411df9 [PubMed: 22257970]
- Newman AB, Naydeck BL, Sutton-Tyrrell K, Polak JF, Kuller LH, Cardiovascular Health Study Research Group. The role of comorbidity in the assessment of intermittent claudication in older adults. *Journal of Clinical Epidemiology*. 2001; 54:294–300. DOI: 10.1016/S0895-4356(00)00308-5 [PubMed: 11223327]
- Ostchega Y, Paulose-Ram R, Dillon CF, Gu Q, Hughes JP. Prevalence of peripheral arterial disease and risk factors in persons aged 60 and older: Data from the National Health and Nutrition Examination Survey 1999–2004. *Journal of the American Geriatrics Society*. 2007; 55:583–589. DOI: 10.1111/j.1532-5415.2007.01123.x [PubMed: 17397438]
- Raftery AE. Bayesian model selection in social research. *Sociological Methodology*. 1995; 25:111–163. DOI: 10.2307/271063
- Rose GA. The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. *Bulletin of the World Health Organization*. 1962; 27:645–658. [PubMed: 13974778]
- Schorr EN, Peden-McAlpine C, Treat-Jacobson D, Lindquist R. Characterization of the peripheral artery disease symptom experience. *Geriatric Nursing*. 2015; 36:293–300. DOI: 10.1016/j.gerinurse.2015.03.004 [PubMed: 25935355]
- Schorr EN, Treat-Jacobson D. Methods of symptom evaluation and their impact on peripheral artery disease (PAD) symptom prevalence: A review. *Vascular Medicine*. 2013; 18:95–111. DOI: 10.1177/1358863X13480001 [PubMed: 23509087]

- Singer, JD., Willett, JB. Applied longitudinal data analysis: Modeling change and event occurrence. New York, NY: Oxford University Press; 2003.
- Stoffers HE, Kester AD, Kaiser V, Rinkens PE, Kitslaar PJ, Knottnerus JA. The diagnostic value of the measurement of the ankle-brachial systolic pressure index in primary health care. *Journal of Clinical Epidemiology*. 1996; 49:1401–1405. DOI: 10.1016/S0895-4356(96)00275-2 [PubMed: 8970490]
- Stoffers HE, Rinkens PE, Kester AD, Kaiser V, Knottnerus JA. The prevalence of asymptomatic and unrecognized peripheral arterial occlusive disease. *International Journal of Epidemiology*. 1996; 25:282–290. DOI: 10.1093/ije/25.2.282 [PubMed: 9119553]
- Stuart RJ Jr, Ellestad MH. National survey of exercise stress testing facilities. *Chest*. 1980; 77:94–97. [PubMed: 7351157]
- Treat-Jacobson D, Bronas UG, Leon AS. Efficacy of arm-ergometry versus treadmill exercise training to improve walking distance in patients with claudication. *Vascular Medicine*. 2009; 14:203–213. DOI: 10.1177/1358863X08101858 [PubMed: 19651669]
- Treat-Jacobson D, Henly SJ, Bronas UG, Leon AS, Henly GA. The pain trajectory during treadmill testing in peripheral artery disease. *Nursing Research*. 2011; 60(Suppl 3):S38–S49. DOI: 10.1097/NNR.0b013e318218600b [PubMed: 21543960]
- Van Beekvelt MC, Borghuis MS, van Engelen BG, Wevers RA, Colier WN. Adipose tissue thickness affects in vivo quantitative near-IR spectroscopy in human skeletal muscle. *Clinical Science*. 2001; 101:21–28. DOI: 10.1042/cs1010021 [PubMed: 11410110]
- Van Beekvelt MC, Colier WN, Wevers RA, Van Engelen BG. Performance of near-infrared spectroscopy in measuring local O₂ consumption and blood flow in skeletal muscle. *Journal of Applied Physiology*. 2001; 90:511–519. [PubMed: 11160049]
- Vardi M, Nini A. Near-infrared spectroscopy for evaluation of peripheral vascular disease. A systematic review of literature. *European Journal of Vascular and Endovascular Surgery*. 2008; 35:68–74. DOI: 10.1016/j.ejvs.2007.07.015 [PubMed: 17919945]
- Wariar R, Gaffke JN, Haller RG, Bertocci LA. A modular NIRS system for clinical measurement of impaired skeletal muscle oxygenation. *Journal of Applied Physiology*. 2000; 88:315–325. [PubMed: 10642395]

Participant 25: Typical Location, Atypical Descriptor (Calf, Burn)

Participant 1: Atypical Location, Atypical Descriptor (Foot, Burn)

FIGURE 1.

Exemplars of changes in tissue saturation index (TSI) relative to classic claudication and atypical symptom reporting during exercise (E) and recovery (R). Panel A illustrates the changes in TSI associated with ischemia during exercise and recovery of a participant exhibiting classic claudication in the calf, using a classic descriptor “ache.” Panel B illustrates the changes in TSI of an individual exhibiting classic claudication in the calf, but using an atypical descriptor “burn.” Panel C illustrates the changes in TSI of an individual exhibiting claudication in an atypical location, foot, and using an atypical descriptor “burn.” NOTE: there are three panels in the figure.

TABLE 1

Participant Characteristics

Characteristic	<i>n</i>	(%)
Age (years)		
49–64	17	(42.5)
65–83	23	(57.5)
Gender (male)	35	(87.5)
Race/ethnicity		
Caucasian	36	(90.0)
African American	2	(5.0)
Native American	2	(5.0)
Education		
High school diploma	9	(22.5)
Some college	16	(40.0)
College degree ^d	15	(37.5)
Employment		
Full-time	5	(12.5)
Homemaker	1	(2.5)
Part-time	8	(20.0)
Retired	26	(65.0)
Marital status		
Married/living with partner	23	(57.5)
Divorced	9	(22.5)
Widowed or single	8	(20.0)
Ankle-brachial index (ABI) ^{b,c}		
Non-compressible (>1.40)	1	(2.5)
Normal (1.00–1.40)	9	(22.5)
Borderline abnormal (0.91–0.99)	5	(12.5)
Mild (0.70–0.90)	6	(15.0)
Moderate (0.50–0.69)	15	(37.5)
Severe (0.49)	4	(10.0)
Body mass index (BMI) ^d		
Underweight (<18.50)	1	(2.5)
Normal weight (18.50–24.99)	10	(25.0)
Overweight (25.00–29.99)	18	(45.0)
Obese (30.00)	11	(27.5)
Smoking		
History	7	(75.0)
Current	30	(17.5)
Never smoked	3	(7.5)
Comorbidities ^e		

Characteristic	<i>n</i>	(%)
Hypertension	37	(92.5)
Hyperlipidemia	36	(90.0)
Osteoarthritis	12	(30.0)
Diabetes type 2	8	(20.0)
Medications ^f		
Anti-hypertensive	35	(87.5)
Anti-platelet	34	(85.0)
Cholesterol-lowering	36	(90.0)

Note. N = 40.

^aIncludes graduate degrees.

^bUsed to index disease severity.

^cFor classification criteria, see Aboyans et al., 2012.

^dFor categorization criteria, see Ardern, Janssen, Ross, & Katzmarzyk, 2004.

^eOther includes type 1 diabetes (n = 2; 5.0%), neuropathy (n = 8; 20%), rhythm disturbance (n = 7; 17.5%), cancer history (n = 4; 10.0%), depression (n = 4; 10.0%), metabolic syndrome (n = 3; 7.5%), anemia history (n = 2; 5.0%), rheumatoid arthritis (n = 2; 5.0%), and spinal stenosis (n = 1; 2.5%).

^fParticipants also used supplements: multivitamins (n = 20; 50.0%), fish oil (n = 12; 30.0%), and iron (n = 2; 5.0%).

TABLE 2
Fixed Effects Estimates of the Predictors of Tissue Saturation Index (TSI) During Exercise and Recovery

Predictor	Exercise			Recovery		
	Est.	(SE)	p	Est.	(SE)	p
Intercept	43.21	(4.73)	<.001	18.89	(9.07)	.04
Exercise time (minutes)	-0.84	(0.12)	<.001	-0.06	(0.18)	.72
Recovery time (minutes)	0.35	(0.05)	<.001	-0.01	(0.09)	.94
Baseline TSI						
NRS Rating 0	0			46.52	(9.55)	<.001
NRS Rating 1 (onset)	-9.58	(0.95)	<.001	38.94	(7.72)	<.001
NRS Rating 2	-9.32	(1.06)	<.001	32.77	(6.00)	<.001
NRS Rating 3	-8.04	(1.14)	<.001	22.62	(4.41)	<.001
NRS Rating 4	-7.10	(1.28)	<.001	16.10	(3.10)	<.001
NRS Rating 5 (maximum)	-6.33	(1.44)	<.001	0		
Time × rating				0.01	(.002)	.003
Baseline TSI × rating				0.06	(.03)	.03
ABI category						
ABI 1.00–1.40	0			0		
ABI 0.91–0.99	0.22	(4.29)	.96	-1.44	(5.80)	.81
ABI 0.70–0.90	-8.10	(4.05)	.05	1.89	(5.48)	.73
ABI 0.50–0.69	8.97	(3.31)	.01	-9.97	(4.47)	.03
ABI 0.49	-14.97	(4.75)	.004	-19.14	(6.39)	.005
ABI > 1.40	-21.87	(8.29)	.01	-25.27	(11.29)	.03
BMI category						
Normal	0			0		
Underweight	0.23	(8.07)	.98	-12.79	(10.84)	.25
Overweight	4.00	(3.21)	.22	6.11	(4.32)	.17
Obese	7.07	(3.56)	.06	9.50	(4.77)	.06

Note. N = 40.

ABI = ankle-brachial index; BMI = body mass index; Est. = estimate; NRS = numerical rating scale; SE = standard error; TSI = tissue saturation index.

TABLE 3

Symptom Descriptors and Locations Provided During Exercise

Descriptor	Location
Ache *	Ankle
Burn	Buttock *
Charley horse	Calf *
Cramp *	Foot
Grinding/rubbing	Groin
Heavy	Hamstring
Knot	Hip
Numb	Knees
Pain *	Quadriceps
Pressure	Shin
Prickly	
Pulling	
Sore	
Tight	
Tingling	
Tired */fatigued	
Twinge	
Warmth	

Note. N = 40.

* Descriptors and locations commonly associated with classic claudication.

TABLE 4

Symptom Descriptors for Maximum Calf Discomfort during Exercise

Descriptor	<i>n</i>	(%)
Tight	28	(33.7)
Ache *	18	(21.7)
Cramp *	18	(21.7)
Pain *	7	(8.4)
Charley horse *	3	(3.6)
Pressure	3	(3.6)
Burn	2	(2.4)
Tired *	2	(2.4)
Fatigued	1	(1.2)
Heavy	1	(1.2)

Note. Percentages are based on the 83 exercise tests stopped due to maximum discomfort in the calf; percentages do not add up to 100% due to rounding.

* Descriptor commonly associated with classic claudication.