4-2024

Peripheral artery disease causes consistent gait irregularities regardless of the location of leg claudication pain

Hafizur Rahman
The University of Texas Rio Grande Valley

Todd Leutzinger

Mahdi Hassan

Molly Schieber

Panagiotis Koutakis

See next page for additional authors

Recommended Citation

Rahman, H., Leutzinger, T., Hassan, M., Schieber, M., Koutakis, P., Fuglestad, M. A., ... & Myers, S. A. (2024). Peripheral artery disease causes consistent gait irregularities regardless of the location of leg claudication pain. Annals of physical and rehabilitation medicine, 67(3), 101793. https://doi.org/10.1016/j.rehab.2023.101793

Annals of Physical and Rehabilitation Medicine 67 (2024) 101793

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Original article

Peripheral artery disease causes consistent gait irregularities regardless of the location of leg claudication pain

Hafizur Rahman[a,b,c], Todd Leutzinger[b], Mahdi Hassan[b,c], Molly Schieber[d], Panagiotis Koutakis[e], Matthew A. Fuglestad[d], Holly DeSpiegelaere[c], G. Matthew Longo[d], Philippe Malcolm[b], Jason M. Johanning[c,d], George P. Casale[d], Iraklis I. Pipinos[c,d], Sara A. Myers[b,c,*]

[a] School of Podiatric Medicine, University of Texas Rio Grande Valley, Harlingen, TX, USA
[b] Department of Biomechanics, University of Nebraska at Omaha, Omaha, NE, USA
[c] Department of Surgery and Research Service, Nebraska-Western Iowa Veterans Affairs Medical Center, Omaha, NE, USA
[d] Department of Surgery, University of Nebraska Medical Center, Omaha, NE, USA
[e] Department of Biology, Baylor University, Waco, TX, USA

ARTICLE INFO

Article History:
Received 9 August 2022
Accepted 1 August 2023

Keywords:
Peripheral artery disease
Claudication
Location of claudication pain
Gait biomechanics

ABSTRACT

Background: The most common symptom of peripheral artery disease (PAD) is intermittent claudication that involves the calf, thigh, and/or buttock muscles. How the specific location of this leg pain is related to altered gait, however, is unknown.
Objectives: We hypothesized that because the location of claudication symptoms uniquely affects different leg muscle groups in people with PAD, this would produce distinctive walking patterns.
Methods: A total of 105 participants with PAD and 35 age-matched older volunteers without PAD (CTRL) were recruited. Participants completed walking impairment questionnaires (WIQ), Gardner-Skinner progressive treadmill tests, the six-minute walk test, and we performed an advanced evaluation of the biomechanics of their overground walking. Participants with PAD were categorized into 4 groups according to their stated pain location(s): calf only (C, n = 43); thigh and calf (TC, n = 18); buttock and calf (BC, n = 15); or buttock, thigh, and calf (BTC, n = 29). Outcomes were compared between CTRL, C, TC, BC and BTC groups using a one-way ANOVA with post-hoc comparisons to identify and assess statistically significant differences.
Results: There were no significant differences between CTRL, C, TC, BC and BTC groups in distances walked or walking speed when either pain-free or experiencing claudication pain. Each participant with PAD had significantly dysfunctional biomechanical gait parameters, even when pain-free, when compared to CTRL (pain-free) walking data. During pain-free walking, out of the 18 gait parameters evaluated, we only identified significant differences in hip power generation during push-off (in C and TC groups) and in knee power absorption during weight acceptance (in TC and BC groups). There were no between-group differences in gait parameters while people with PAD were walking with claudication pain.
Conclusions: Our data demonstrate that PAD affects the ischemic lower extremities in a diffuse manner irrespective of the location of claudication symptoms.
Database Registration: ClinicalTrials.gov NCT01970332.

Introduction

Peripheral artery disease (PAD) is an atherosclerotic occlusive disease of the arteries supplying the lower extremities. The most common symptom of PAD is intermittent claudication, defined as debilitating pain involving the muscles of the calves, thighs, and/or buttocks that is produced by walking and relieved with rest. Claudication causes people with PAD to walk more slowly and have impaired gait biomechanics, including altered joint angles, reduced

Abbreviations: 6MWT, six-minute walk test; BC, participants with peripheral artery disease with buttock and calf claudication pain; BTC, participants with peripheral artery disease with buttock, thigh, and calf claudication pain; C, participants with peripheral artery disease with calf claudication pain; CTRL, age-matched individuals without peripheral artery disease/claudication (control subjects); PAD, peripheral artery disease; STROBE, strengthening reporting of observational studies in epidemiology; TC, participants with peripheral artery disease with thigh and calf claudication pain; WIQ, walking impairment questionnaire

* Corresponding author at: Department of Biomechanics, University of Nebraska at Omaha, 6160 University Dr S, Omaha, NE 68182, USA.
E-mail address: samyers@unomaha.edu (S.A. Myers).

https://doi.org/10.1016/j.rehab.2023.101793

joint torque, reduced power at the ankle, knee, and hip joints, and it reduces their quality of life [1–9]. The abnormal biomechanics are detectable in the first steps people take after developing PAD, often well before the onset of claudication pain [3,4].

We know very little about the effects of the location (calf/thigh/buttock) of leg symptoms on these abnormal biomechanical parameters. A recent study by Guilleron et al. investigated the effect of the location of ischemia and ischemic pain on spatiotemporal parameters and muscle activity during treadmill walking in people with PAD and claudication [10]. The results suggested that people with PAD who had proximo-distal symptoms (localized both in the calf and the thigh and/or buttock) walked less, with increased step length and step time, and reduced cadence compared to people with PAD with distal symptoms (localized in the calf). Furthermore, people with PAD and proximo-distal symptoms had lower tibialis anterior muscle activation peak and activation time compared to people with PAD and distal symptoms [10].

Investigating the effects of the location of claudication pain on gait patterns may provide important knowledge regarding the degree of functional limitation and the type of adjustments employed by people with PAD. This knowledge may help to develop treatment plans that target specific muscle groups, such as in the ankle, knee, or hip flexors/extensors, based on the pattern of limitations associated with the location of claudication pain. It may also provide the basis for physical therapy and exercise intervention guidelines that are more person-specific and so effective. Therefore, in this study, we tested the hypothesis that the location of symptoms uniquely affects different leg muscle groups of people with PAD and produces distinctive patterns in the way people with claudication walk. Participants with PAD were placed into 4 groups, based on the location of their claudication pain. Inter-group data from quality-of-life questionnaires, distances walked, gait kinematics and kinetics were compared. In addition, each PAD group was compared to a control group of individuals who did not have PAD or claudication pain to provide comparison data for quality-of-life questionnaires, and gait kinematics and kinetics.

Methods

Participants and ethical considerations

The study was approved by the Institutional Review Boards at Nebraska Western Iowa Veteran Affairs Medical Center and the University of Nebraska Medical Center in the United States. A total of 105 participants with PAD (Fontaine Stage II) and claudication were recruited through the vascular surgery clinics of the institutions. Each participant with PAD had an ankle-brachial index ≤0.90 at rest, stable blood pressure, and had lipid, and/or diabetes regimen risk factors controlled for ≥6 weeks. Participants with PAD were excluded if they had any gait-altering musculoskeletal or neurological conditions that significantly limited or affected their gait. Participants' history and physical examinations were evaluated by 1 of 2 board-certified vascular surgeons.

A total of 35 older individuals without PAD were recruited as controls from the surrounding community. Control participants were excluded if they had any walking limitations or if they experienced any leg pain during walking. Informed consent was obtained from all subjects prior to participation in the study, according to the guidelines of the institutions' review boards.

Experimental procedures and data collection

Experimental tests were performed at the Biomechanics Research Building at the University of Nebraska at Omaha. Upon arrival at the laboratory, each participant's age, height, and body mass were recorded. Participants completed the tests in the following order: (i) Walking Impairment Questionnaire (WIQ), (ii) Gardner-Skinner progressive treadmill test [11], (iii) Six-minute walk test (6MWT), and (iv) Overground biomechanics walking tests. Controls did not do the Gardner-Skinner progressive treadmill test or the 6MWT.

(i) Walking Impairment Questionnaire (WIQ)

The WIQ is a validated questionnaire for evaluating subjective walking ability in people with PAD [12,13]. Each participant completed the 4 subsections: pain, distance, walking speed, and stair climbing. Each subsection score ranges from 0 to 100 (where 0 is the worst, and 100 is the best health status).

(ii) Gardner-Skinner progressive treadmill test

The Gardner-Skinner progressive treadmill test involves participants with PAD walking on a treadmill at a speed of 2 mph (0.89 m/s) beginning on a 0 % gradient (level) and increasing by 2 % every 2 min [11]. Initial and absolute 'claudication distances' were calculated: the initial claudication distance was recorded at the first indication of claudication pain, and absolute claudication distance was the point at which claudication pain forced participants to stop walking.

(iii) Six-minute walk test (6MWT)

To conduct the 6MWT, 2 cones were placed 50 feet (15.24 m) apart in the gait analysis laboratory. Participants with PAD were asked to cover as much distance between the cones as possible in 6 min; they were told that they could stop and rest if necessary during the test. The total distance walked in 6 min was recorded as the 6MWT distance [14,15]. After the Gardner-Skinner treadmill test, participants with PAD rested for ≤15 min (as required) to ensure that they did not have claudication pain before starting the 6MWT.

(iv) Overground biomechanics walking tests

Prior to the walking tests, 27 retro-reflective markers were placed at specific anatomical locations on each participant's lower limbs, as previously described [1–4]. For the overground trials, participants walked at a self-selected pace across a 10-meter pathway containing a force platform set level with the floor. Lower extremity 3-dimensional kinematics and kinetics data were recorded using a 12 high-speed infrared camera system (60 Hz, Motion Analysis Corporation, Rohnert Park, CA) and force platforms (600 Hz, AMTI, Watertown, MA).

Participants with PAD performed overground walking trials in both pain-free conditions and when in claudication pain. Controls performed only in pain-free condition, since inclusion criteria included that they did not have any pain associated with walking. During the pain-free trials, participants with PAD had to have at least mandatory 1-min rest between each trial to ensure the absence of claudication pain. To induce claudication pain, participants with PAD performed the Gardner-Skinner progressive treadmill test. As soon as they felt the onset of claudication pain, participants started to perform the overground walking trials. During claudication pain, participants did not rest between trials in order to maintain their claudication pain.

Data analysis

Raw test outputs were used for all measures except for the overground trials, which required further processing to calculate the lower extremity gait biomechanics parameters. For kinematic and kinetic data, a total of 5 clean foot contacts were collected and

Table 1
Demographic and clinical characteristics of participants with peripheral artery disease (PAD), grouped by where the location of claudication pain in their leg muscles, and control subjects without PAD.

Characteristics	Control (CTRL) (*N* = 35)	Location of Claudication Pain			
		Calf (C) (*N* = 43)	Thigh and calf (TC) (*N* = 18)	Buttock and calf (BC) (*N* = 15)	Buttock, thigh and calf (BTC) (*N* = 29)
Age (years)	65.2 (9.5)	63.6 (5.9)	62.3 (7.3)	65.2 (7.0)	62.5 (6.6)
Sex	29 M, 6F	42 M, 1F	18M	15M	29M
Body mass (kg)	79.9 (13.8)	84.2 (16.6)	88.0 (17.5)	93.2 (20.7)	86.9 (14.4)
Height (m)	1.7 (0.1)	1.8 (0.1)	1.8 (0.1)	1.8 (0.1)	1.8 (0.1)
Body mass index (kg/m^2)	26.4 (3.7)	27.3 (4.3)	28.9 (7.3)	30.3 (6.9)	27.8 (4.0)
Ankle-brachial index*	>0.9	0.5 (0.2)	0.5 (0.2)	0.5 (0.2)	0.5 (0.2)

Values are reported as mean (standard deviation).
* The ABI is the ratio between the systolic blood pressure of the ankle, and of an upper extremity.

averaged for each participant in each condition. A clean foot contact was defined as when 1 leg completely landed on a single force plate during the stance phase with no other contact on that force plate during the walking trial. Joint kinematic and kinetic data (range of motion, torque, and power for ankle, knee, and hip joints) were calculated in the sagittal plane during the stance phase from the overground trials, as previously described [1–4]. The kinetic data during the stance phase were further divided into 3 distinct stages: weight acceptance, single leg support, and push-off. Walking speed was calculated as the average distance traveled per second based on the coordinates of the reflective markers from the overground biomechanics walking test, as previously described [5,6]. Walking speed was calculated for participants with PAD in both pain-free and claudication-pain conditions. For controls, only pain-free walking speed was calculated as they had no claudication pain and only performed the overground walking test in a pain-free condition. All analyses were performed using MATLAB (MathWorks, Natick, MA) and Visual3D (C-Motion, Inc., Germantown, MD) software. Data were expressed in means and standard deviation for all variables.

Participants with PAD were categorized into 4 groups according to the stated location of pain by participants in their clinical records; this categorization was confirmed by notes from data collection sessions: (i) C (calf-only claudication), (ii) TC (claudication pain in thigh and calf), (iii) BC (claudication pain in buttock and calf), and (iv) BTC (claudication pain in buttock, thigh, and calf). Outcomes were compared for controls (CTRL), C, TC, BC and BTC groups using a one-way ANOVA with post-hoc comparisons (Tukey honestly significant difference) to assess statistically significant differences between groups. Statistical comparisons were performed using SPSS software (version 26, IBM, Armonk, NY). The level of significance was set at 0.05. The study is reported according to the Strengthening Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Results

Participant demographics

Out of 105 participants with PAD, 43 had claudication pain in their calf, 18 had pain in their thigh and calf, 15 had pain in their buttock and calf, and 29 had claudication pain in their buttock, thigh, and calf. There were no significant intergroup differences among CTRL, C, TC, BC and BTC groups in age or body mass index (Table 1). Differences in ankle-brachial index values between the 4 PAD groups were also not significant (Table 1).

WIQ scores

Participants with PAD from each group (C, TC, BC and BTC) had significantly lower WIQ scores compared to CTRL for all 4 subsections (pain, distance, walking speed, and stair climbing) (Table 2). For the WIQ subsections' scores for the same groups, the C group had a significantly higher WIQ score for pain than the BTC group (P = 0.035). Otherwise, there were no other significant differences in distance, walking speed, and stair climbing subsection scores in the C, TC, BC and BTC groups (Table 2).

Walking distances

There were no statistically significant inter-group differences in either initial or absolute claudication distances between C, TC, BC and

Table 2
Walking Impairment Questionnaire (WIQ) subscale scores for participants with peripheral arterial disease (PAD), grouped by where they experienced localized claudication pain in their leg muscles, and age-matched control subjects without PAD.

WIQ Subscale*	Control (N = 35)	Location of Claudication Pain			
		Calf (C) (N = 43)	Thigh and calf (TC) (N = 18)	Buttock and calf (BC) (N = 15)	Buttock, thigh and calf (BTC) (N = 29)
1. Pain	95.7 (8.5)[b,c,d,e]	55.5 (21.0)[a,e]	52.8 (12.5)[a]	53.3 (31.2)[a]	40.6 (23.5)[a,b]
2. Distance	92.2 (15.9)[b,c,d,e]	25.5 (26.7)[a]	23.0 (20.5)[a]	19.6 (23.6)[a]	14.8 (18.9)[a]
3. Walking Speed	80.4 (18.9)[b,c,d,e]	29.4 (24.1)[a]	36.7 (18.8)[a]	24.1 (24.2)[a]	30.4 (28.3)[a]
4. Stair Climbing	92.1 (15.9)[b,c,d,e]	39.7 (26.7)[a]	48.2 (28.2)[a]	29.2 (28.5)[a]	28.7 (21.5)[a]

* The 4 WIQ subscale scores each range from 0 (worst health status) to 100 (best health status). All values are reported as mean (standard deviation); Group data were analyzed using a one-way ANOVA with post-hoc comparisons (see text) and a significant result was P<0.05.
[a] significantly different to CTRL group.
[b] significantly different to C group.
[c] significantly different to TC group.
[d] significantly different to BC group.
[e] significantly different to BTC group.

Table 3
Walking distances of study participants with peripheral artery disease (PAD) who were in groups according to location of claudication pain in their leg muscles. Assessments used included the six-minute walking test (6MWT) and the Gardner-Skinner progressive treadmill test.

Distance walked (meters)	Location of Claudication Pain			
	Calf (C) (*N* = 43)	Thigh and calf (TC) (*N* = 18)	Buttock and calf (BC) (*N* = 15)	Buttock, thigh and calf (BTC) (*N* = 29)
Gardner-Skinner progressive treadmill test				
Initial claudication	84.9 (44.7)	77.2 (52.2)	79.9 (58.1)	78.8 (50.5)
Absolute claudication	259.2 (154.0)	257.9 (174.9)	211.6 (110.8)	238.1 (95.9)
6MWT	309.2 (77.1)	285.0 (84.5)	292.4 (84.6)	312.4 (86.4)

Values are reported as Mean (Standard deviation); Initial claudication, distance walked until the first reported sensation of claudication; Absolute claudication, distance walked until claudication pain forced participants to stop.

BTC groups (Table 3). Similarly, each of the groups walked similar 6MWT distances irrespective of the location of claudication pain (Table 3).

Gait biomechanics during pain-free walking

There were no significant differences among CTRL, C, TC, BC and BTC results for walking speed during pain-free walking (Table 4). Significant gait dysfunctions were observed in C, TC, BC and BTC groups compared to the CTRL group during pain-free walking (Table 4). Out of the 18 gait parameters measured, 2 were significantly different in all PAD groups compared to CTRL data. The number of gait parameters that were significantly altered (when compared to CTRL data) was greatest in C and BTC groups (11 out of 18 comparisons) and fewest in TC group (2 of 18 comparisons).

During push-off, ankle power generation significantly decreased by 30 % (C; $P < 0.001$), 23 % (TC; $P = 0.003$), 29 % (BC; $P < 0.001$) and 28 % (BTC; $P < 0.001$) in people with PAD, compared to the CTRL group. Knee power absorption during push-off was also decreased in C, TC, BC and BTC groups (Table 4). The C group participants generated 22 % less hip power during push-off compared to those in the TC group ($P = 0.022$). The BC group participants' knee absorption power was reduced during weight acceptance when compared to TC group data ($P = 0.01$) (Table 4).

Gait biomechanics during walking with claudication pain

We did not find any statistically significant differences in walking speed for CTRL participants during pain-free walking to people in the C, TC, BC and BTC groups during walking with claudication pain, (Table 5). The groups all had similar walking speeds during claudication pain. However, all C, TC, BC and BTC participants had significant gait dysfunctions when walking with claudication pain compared to CTRL data (during pain-free walking) (Table 5): the BTC group had the greatest number of altered gait parameters (13 out of 18 comparisons), and the TC group had the fewest (7 of 18 comparisons). Six gait parameters were significantly altered in C, TC, BC and BTC groups compared to CTRL: ankle plantar flexor torque, hip flexor torque, ankle power absorption during weight acceptance, and ankle power generation, knee power absorption, and hip power generation during push-off.

Table 4
Gait biomechanical parameters for participants with peripheral arterial disease (PAD), grouped by where they experienced localized claudication pain in their leg muscles, and age-matched control subjects without PAD, during pain-free walking assessments.

Gait Parameter	Control (CTRL) (N = 35)	Location of Claudication Pain			
		Calf (C) (N = 43)	Thigh and calf (TC) (N = 18)	Buttock and calf (BC) (N = 15)	Buttock, thigh and calf (BTC) (N = 29)
Walking speed (m/s)	1.09 (0.19)	1.08 (0.18)	1.21 (0.11)	1.16 (0.23)	1.09 (0.16)
Ankle dorsiflexor torque (Nm/kg)	− 0.32 (0.10)[b]	− 0.24 (0.09)[a]	− 0.29 (0.11)	− 0.25 (0.09)	− 0.26 (0.11)
Ankle plantar flexor torque (Nm/kg)	1.38 (0.19)	1.29 (0.15)	1.27 (0.19)	1.26 (0.17)	1.31 (0.18)
Knee extensor torque (Nm/kg)	0.69 (0.21)[d,e]	0.53 (0.26)	0.60 (0.31)	0.38 (0.30)[a]	0.46 (0.21)[a]
Knee flexor torque (Nm/kg)	− 0.14 (0.15)	− 0.16 (0.16)	− 0.18 (0.14)	− 0.25 (0.21)	− 0.22 (0.17)
Hip extensor torque (Nm/kg)	0.85 (0.29)[b,e]	0.62 (0.21)[a]	0.69 (0.21)	0.73 (0.21)	0.62 (0.24)[a]
Hip flexor torque (Nm/kg)	− 1.05 (0.21)[b,d,e]	− 0.78 (0.24)[a]	− 0.89 (0.21)	− 0.79 (0.28)[a]	− 0.77 (0.25)[a]
Ankle power absorption during weight acceptance (W/kg)	− 0.67 (0.29)[b,d,e]	− 0.45 (0.20)[a]	− 0.51 (0.24)	− 0.42 (0.17)[a]	− 0.42 (0.20)[a]
Ankle power absorption during single leg support (W/kg)	− 0.83 (0.25)	− 0.79 (0.25)	− 0.81 (0.26)	− 0.89 (0.33)	− 0.81 (0.27)
Ankle power generation during push-off (W/kg)	2.70 (0.69)[b,c,d,e]	1.90 (0.53)[a]	2.07 (0.56)[a]	1.91 (0.49)[a]	1.95 (0.60)[a]
Knee power absorption during weight acceptance (W/kg)	− 0.91 (0.39)[b,d,e]	− 0.64 (0.38)[a]	− 0.83 (0.32)[d]	− 0.41 (0.29)[a,c]	− 0.57 (0.33)[a]
Knee power generation during single leg support (W/kg)	0.45 (0.22)[b,d,e]	0.31 (0.18)[a]	0.33 (0.24)	0.26 (0.21)[a]	0.24 (0.12)[a]
Knee power absorption during push-off (W/kg)	− 1.19 (0.47)[b,c,d,e]	− 0.74 (0.30)[a]	− 0.89 (0.35)[a]	− 0.77 (0.30)[a]	− 0.73 (0.29)[a]
Hip power generation during weight acceptance (W/kg)	0.41 (0.29)	0.38 (0.25)	0.35 (0.27)	0.56 (0.34)	0.39 (0.34)
Hip power absorption during single leg support (W/kg)	− 0.84 (0.26)[b,d,e]	− 0.59 (0.24)[a]	− 0.66 (0.28)	− 0.56 (0.36)[a]	− 0.60 (0.32)[a]
Hip power generation during push-off (W/kg)	0.99 (0.23)[b,d,e]	0.68 (0.22)[a,c]	0.87 (0.24) [b]	0.75 (0.24)[a]	0.71 (0.19)[a]
Ankle range of motion (degree)	18.78 (3.66)	19.72 (3.07)	18.87 (3.85)	20.35 (3.39)	19.60 (4.06)
Knee range of motion (degree)	12.21 (3.67)	10.96 (5.34)	12.34 (5.12)	10.36 (4.76)	10.77 (3.73)
Hip range of motion (degree)	40.10 (3.27)[b,e]	35.69 (5.19)[a]	38.71 (4.82)	36.82 (6.07)	35.98 (4.11)[a]

Values are reported as mean (standard deviation); m/s, meters per second; Nm/kg, Newton-meters per kilogram; W/kg, watts per kilogram; Group data were analyzed using a one-way ANOVA with post-hoc comparisons (see text) and a significant result was $P<0.05$.

[a] significantly different to CTRL group.
[b] significantly different to C group.
[c] significantly different to TC group.
[d] significantly different to BC group.
[e] significantly different to BTC group.

Table 5
Gait biomechanics for participants with peripheral arterial disease (PAD), grouped by the location of claudication pain in their leg muscles. Participants were assessed during walking while experiencing claudication pain. Data were compared to age-matched control subjects without PAD who walked without pain.

Gait Parameter	Control (N = 35)	Location of Claudication Pain			
		Calf (C) (N = 43)	Thigh and calf (TC) (N = 18)	Buttock and calf (BC) (N = 15)	Buttock, thigh and calf (BTC) (N = 29)
Walking speed (m/s)	1.09 (0.19)	1.05 (0.22)	1.16 (0.13)	1.11 (0.24)	1.06 (0.17)
Ankle dorsiflexor torque (Nm/kg)	− 0.32 (0.10)[b,d,e]	− 0.25 (0.11)[a]	− 0.24 (0.09)	− 0.23 (0.08)[a]	− 0.23 (0.08)[a]
Ankle plantar flexor torque (Nm/kg)	1.38 (0.19)[b,c,d,e]	1.19 (0.22)[a]	1.20 (0.19)[a]	1.19 (0.21)[a]	1.23 (0.22)[a]
Knee extensor torque (Nm/kg)	0.69 (0.21)[d,e]	0.57 (0.25)	0.55 (0.24)	0.39 (0.29)[a]	0.50 (0.20)[a]
Knee flexor torque (Nm/kg)	− 0.14 (0.15)	− 0.17 (0.20)	− 0.19 (0.23)	− 0.23 (0.21)	− 0.22 (0.18)
Hip extensor torque (Nm/kg)	0.85 (0.29)[b,c,e]	0.63 (0.23)[a]	0.65 (0.21)[a]	0.73 (0.23)	0.60 (0.23)[a]
Hip flexor torque (Nm/kg)	− 1.05 (0.21)[b,c,d,e]	− 0.73 (0.27)[a]	− 0.82 (0.20)[a]	− 0.78 (0.28)[a]	− 0.73 (0.25)[a]
Ankle power absorption during weight acceptance (W/kg)	− 0.67 (0.29)[b,c,d,e]	− 0.46 (0.24)[a]	− 0.46 (0.22)[a]	− 0.39 (0.17)[a]	− 0.39 (0.20)[a]
Ankle power absorption during single leg support (W/kg)	− 0.83 (0.25)	− 0.84 (0.31)	− 0.83 (0.28)	− 0.97 (0.44)	− 0.81 (0.31)
Ankle power generation during push-off (W/kg)	2.70 (0.69)[b,c,d,e]	1.66 (0.57)[a]	1.83 (0.58)[a]	1.74 (0.58)[a]	1.65 (0.57)[a]
Knee power absorption during weight acceptance (W/kg)	− 0.91 (0.39)[d,e]	− 0.68 (0.42)	− 0.74 (0.38)	− 0.41 (0.29)[a]	− 0.59 (0.31)[a]
Knee power generation during single leg support (W/kg)	0.45 (0.22)[d,e]	0.34 (0.21)	0.33 (0.20)	0.24 (0.21)[a]	0.27 (0.12)[a]
Knee power absorption during push-off (W/kg)	− 1.19 (0.47)[b,c,d,e]	− 0.69 (0.33)[a]	− 0.81 (0.37)[a]	− 0.72 (0.33)[a]	− 0.69 (0.31)[a]
Hip power generation during weight acceptance (W/kg)	0.41 (0.29)	0.35 (0.24)	0.33 (0.23)	0.56 (0.38)	0.34 (0.24)
Hip power absorption during single leg support (W/kg)	− 0.84 (0.26)[b,d,e]	− 0.60 (0.26)[a]	− 0.73 (0.25)	− 0.58 (0.41)[a]	− 0.63 (0.32)[a]
Hip power generation during push-off (W/kg)	0.99 (0.23)[b,c,d,e]	0.62 (0.24)[a]	0.75 (0.25)[a]	0.75 (0.26)[a]	0.67 (0.23)[a]
Ankle range of motion (degree)	18.78 (3.66)[b,d]	21.59 (3.49)[a]	20.96 (4.74)	22.36 (4.45)[a]	20.93 (3.68)
Knee range of motion (degree)	12.21 (3.67)	11.85 (5.26)	12.11 (5.80)	11.06 (5.19)	11.57 (3.62)
Hip range of motion (degree)	40.10 (3.27)[b,e]	35.49 (5.62)[a]	37.48 (4.77)	36.59 (5.50)	35.26 (4.92)[a]

Values are reported as mean (standard deviation); m/s, meters per second; Nm/kg, Newton-meters per kilogram; W/kg, watts per kilogram; Group data were analyzed using a one-way ANOVA with post-hoc comparisons (see text) and a significant result was $P<0.05$.
[a] significantly different to CTRL group.
[b] significantly different to C group.
[c] significantly different to TC group.
[d] significantly different to BC group.
[e] significantly different to BTC group.

Between the 4 study groups of people with PAD, no significant inter-group differences for any gait parameter were observed (Table 5).

Discussion

In this study, we aimed to test the hypothesis that the location of symptoms uniquely affects different leg muscle groups in people with PAD and that the resultant claudication produces distinctive patterns in the way they walk. We evaluated our participants using the walking impairment questionnaire, measurements of walking distances, and advanced biomechanical analysis. Our data indicate that although people with PAD and claudication present with symptoms in different patterns of muscle groups in their lower limb, they walk with a similar degree of impairment across all muscle groups of the leg and that this is observable in their walking patterns and walking distances. While comparing WIQ scores, except for differences in the pain subsection scores between C and BTC groups, there were no significant differences in distance, walking speed, or stair climbing subsection scores among C, TC, BC and BTC group scores. These results suggest that all participants with PAD had similar limitations in functional WIQ activities, despite claudication pain at different locations corresponding to different muscle groups. Furthermore, we found that the 4 groups with PAD had similar initial and absolute claudication distances, as measured with the Gardner-Skinner progressive treadmill test, and that this was also true for the self-paced, 6MWT distance. These results indicate that the participants with PAD in each group all had similar walking distance limitations, irrespective of the group(s) of leg muscles affected by claudication pain.

Walking speed

Our results suggest that participants with PAD from each study group (C, TC, BC and BTC) had similar walking speeds when pain-free and during claudication pain. Previous studies showed that people with PAD walked more slowly than control individuals [6,15]. Interestingly, we did not observe any significant differences in walking speeds between CTRL and PAD group participants: the age-matched individuals recruited as controls had similar walking speed to those in the study groups. Therefore, our findings in this study, including the lower extremity gait biomechanical parameters we calculated, are independent of walking speed. Our group has previously demonstrated that reduced ankle power generation in late stance in people with PAD is independent of walking speed [5]. Future studies should investigate the effects of walking speed on lower extremity gait biomechanics in people with PAD and correlations to the locations of the occlusive disease and claudication symptoms.

Gait biomechanics

The data produced by our advanced biomechanical analysis confirms previous findings that people with PAD have significant gait dysfunction compared to CTRL data while walking both pain-free and with claudication pain. Earlier studies from our group and others have described similar gait dysfunctions in people with PAD in more detail [1–4,16–19]. Interestingly, minimal differences in gait biomechanics existed for all in the study who presented with pain in different components of the leg. During pain-free walking, only 2 out of 18 gait parameters were different across C, TC, BC and BTC groups, and none of the 18 comparisons recorded during painful walking differed. These findings show that people with PAD walk with an abnormal gait pattern both before and after the onset of the claudication pain, and that this pattern is mostly independent of the location of claudication symptoms.

Comparing the walking patterns during the claudication pain condition, all participants with PAD demonstrated significantly decreased knee power absorption during push-off compared to controls, but there were no differences among C, TC, BC and BTC participants. Power around the knee joint is primarily produced by the

posterior thigh muscles; participants with PAD who have claudication that involves the thigh muscles (TC and BTC groups) might be expected to have less knee power compared to those with PAD who have claudication only in the calf (C group). However, this was not reflected in our results: C group participants had similar knee power during push-off compared to TC and BTC group participants. This was also true for hip power during push-off: all of those with PAD generated significantly less hip power during push-off compared to controls and there were no significant differences within the 4 study groups. Hip power is primarily produced by the buttock muscles. Therefore, it was anticipated that participants with claudication involving the buttock muscles (the BC and BTC groups) would have reduced hip power during push-off compared to those whose claudication symptoms did not involve their buttocks (C and TC groups). However, this was not the case: BC and BTC groups had similar hip power results to C and TC groups during push-off.

Claudication pain worsens gait biomechanics

Gait biomechanical parameters were altered in people in the TC, BC and BTC groups, compared to controls, even during pain-free walking, and this increased when they walked with claudication pain. The number of altered gait parameters increased from 2 to 7 for the TC group, from 9 to 12 for the BC group, and 11 to 13 for the BTC group as participants with PAD walked with claudication pain compared to pain-free. For those in the C group, 11 gait parameters were altered compared to CTRL during both pain-free and painful walking. Overall, our results suggest that gait biomechanics deteriorated as the participants in TC, BC and BTC groups progressed from walking without claudication, to walking with claudication symptoms. This is in line with existing literature as previous studies have shown that several gait parameters worsen after the onset of claudication pain [3,4]. Studies have also shown that gait variability for people with PAD is abnormal while walking before the onset of claudication symptoms, and that this increases during walking with pain [20,21]. Several gait variability parameters including standard deviation and approximate entropy increased at knee and hip levels when people with PAD walked with claudication pain [20].

PAD affects ischemic legs in a diffuse manner

Overall, our results demonstrate that people with PAD have similar limitations in quality-of-life parameters, walkable distances, and degrees of gait impairment regardless of the location of claudication pain and the muscle group(s) affected by the claudication symptoms. These data suggest that, while PAD does result in certain muscle groups having more symptoms than others, the disease has a multilevel nature and that diffusely affects the function of all muscle groups in ischemic lower limbs. More specifically, contrary to our original hypothesis, our data demonstrated that PAD impaired the performance of all leg muscles in the buttock, thigh, and calf in the same way, irrespective of the fact that one muscle group was more symptomatic than the others and thus resulted in similar patterns of abnormal gait biomechanics at the ankle, knee, and hip joints.

Our findings of a diffuse effect of PAD on affected limbs are supported by large animal studies: occlusion of the superficial femoral artery in swine produces ischemia that affects not only the calf muscles, but also the muscles of the thigh (biceps femoris, semimembranosus and semitendinosus were evaluated) and buttocks (the gluteus muscles) [22]. It is possible that asymptomatic segments of the leg with claudication are also affected by variable degrees of ischemia and so, despite the absence of symptoms, they malfunction and produce the generalized pattern of failure seen in our data. This possibility is supported by a previous study by Gardner et al. which compared calf muscle hemoglobin oxygen saturation variables among 3 groups of people with PAD who presented with different types of exertional leg pain: atypical exertional leg pain, typical claudication symptoms, and leg pain on exertion and rest [23]. Participants with atypical leg pain were defined as having pain located in the buttocks or thighs, or pain that did not force them to slow down/stop during exercise. Interestingly, calf muscle oxygen saturation variables (resting oxygen saturation, minimum oxygen saturation during exercise, and time to reach minimum oxygen saturation) were not significantly different among the 3 groups. Additionally, the atypical leg pain group had similar calf muscle oxygen saturation variables compared to the group presenting with typical claudication. The investigators concluded that people with PAD have similar declines in microcirculation in the ischemic legs during exercise, irrespective of the different type and location of symptoms [23]. Another recent study by Leutzinger et al. investigated how different levels of stenosis/occlusion (aortoiliac, femoropopliteal, or multi-level) affected walking performance in people with PAD [15]. As for our results, these authors demonstrated that despite different levels of vascular stenosis/occlusion, the participants with PAD had similar gait patterns, walking distances, and subjective impairments. They concluded that PAD affects legs with claudication in a diffuse manner, irrespective of the level of the arterial tree primarily involved [15].

Finally, it is important to consider the, thus far poorly explored, effects of PAD on the rest of the body, as mediated through the activation of metabolic, neural, or inflammatory pathways. These effects may also explain some of our findings since the ischemic limb distributes to, and communicates with, the rest of the body. Thus an adverse ischemic event occurs several times per day, even if every time the patient may not experience associated claudication symptoms. Specifically, people with PAD and calf claudication can not only experience pathological changes and decreased performance of the ipsilateral non-symptomatic thigh or pelvic musculature, but also damage to other limbs and organs of the body. This may represent an important pathway explaining how PAD can produce the increased morbidity and mortality that is so well-documented for people with PAD [24–26]. Some of the strongest evidence for a systemic effect of PAD comes from work showing that a single bout of exercise in legs with PAD produces a significant increase in biomarkers of oxidative stress such as increased malondialdehyde, greater consumption of anti-oxidants [27], and signs of inflammation such as raised neutrophil (and other white blood cells) titres [28,29], and concentrations of cytokines like thromboxane, p-selectin, and von Willebrand factor in the blood. In addition, well-designed studies have also shown that it only takes a few, low-intensity, contractions of the posterior calf muscles of people with PAD to produce a significant sympathetic nervous system activation and adverse effects on physiological parameters like heartrate, blood pressure, and coronary and renal artery blood flows [30–32]. It is also possible that activation of the sympathetic nervous system by calf muscle ischemia can adversely affect blood flow to, and the health of, the thigh and buttock muscles [33,34], something else that would also help to explain the findings of our work.

Limitations

There are limitations to this study. We investigated only the effect of location of claudication symptoms on walking impairment in participants with PAD. It is possible that distances walked and the gait biomechanical parameters may have been altered due to an interaction between the locations of the source occlusive disease and resultant claudication symptoms. We used a 50 feet (15.24 m) walking course for the 6MWT but better reliability has been reported when a walking course between 20 and 30 m is used [35]. Additionally, the kinematic and kinetic analyses were limited to only the lower extremities. It is possible that movement of the trunk and kinematics in upper extremities could also be altered in people with PAD. Future studies should include the measurement of muscle oxygenation, activation, and forces to provide a better understanding of the

neuromuscular responses and the way they relate to the location of claudication symptoms and level of arterial occlusions.

Conclusion

Our data, which included quality-of-life questionnaire results, walking distances, and gait biomechanics, suggests that people with PAD and claudication have a similar quality of life and walking pattern regardless of whether their claudication symptoms are located in the calves, thighs, or buttocks of affected lower limbs. These findings indicate that PAD is, by nature, a multilevel disease: it impacts on the function of the leg muscles in a diffuse manner, generating similar walking impairments irrespective of the muscle group(s) affected by claudication symptoms. Several pathophysiological parameters related to PAD as a multilevel disease including hemodynamics, neuropathy, myopathy, and systemic effects, need further research to understand the complicated and diffuse manner by which claudication and PAD affects the legs of people with this disorder.

Data availability

Data will be made available on request.

Acknowledgments

This work was supported by grants from the National Institute of Health (R01AG034995, R01HD090333, R01AG049868), the United States Department of Veterans Affairs Rehabilitation Research and Development Service (I01RX000604, I01RX003266) and with resources and the use of facilities at the VA Nebraska-Western Iowa Health Care System.

References

[1] Chen SJ, Pipinos I, Johanning J, Radovic M, Huisinga JM, Myers SA, et al. Bilateral claudication results in alterations in the gait biomechanics at the hip and ankle joints. J Biomech 2008;41:2506–14. doi: 10.1016/j.jbiomech.2008.05.011.
[2] Celis R, Pipinos II, Scott-Pandorf MM, Myers SA, Stergiou N, Johanning JM. Peripheral arterial disease affects kinematics during walking. J Vasc Surg 2009;49:127–32. doi: 10.1016/j.jvs.2008.08.013.
[3] Koutakis P, Johanning JM, Haynatzki GR, Myers SA, Stergiou N, Longo GM, et al. Abnormal joint powers before and after the onset of claudication symptoms. J Vasc Surg 2010;52:340–7. doi: 10.1016/j.jvs.2010.03.005.
[4] Koutakis P, Pipinos II, Myers SA, Stergiou N, Lynch TG, Johanning JM. Joint torques and powers are reduced during ambulation for both limbs in patients with unilateral claudication. J Vasc Surg 2010;51:80–8. doi: 10.1016/j.jvs.2009.07.117.
[5] Wurdeman SR, Koutakis P, Myers SA, Johanning JM, Pipinos II, Stergiou N. Patients with peripheral arterial disease exhibit reduced joint powers compared to velocity-matched controls. Gait Posture 2012;36:506–9. doi: 10.1016/j.gaitpost.2012.05.004.
[6] Rahman H, Anderson CP, Pipinos II, Johanning JM, Casale GP, Dong J, et al. Muscle forces and power are significantly reduced during walking in patients with peripheral artery disease. J Biomech 2022;135. doi: 10.1016/J.JBIOMECH.2022.111024.
[7] Rahman H, Pipinos II, Johanning JM, Casale G, Williams MA, Thompson JR, et al. Claudicating patients with peripheral artery disease have meaningful improvement in walking speed after supervised exercise therapy. J Vasc Surg 2021;74(6):1987–95. doi: 10.1016/J.JVS.2021.04.069.
[8] Correia MA, Silva GO, Longano P, Trombetta IC, Consolim-Colombo F, Puech-Leão P, et al. In peripheral artery disease, diabetes is associated with reduced physical activity level and physical function and impaired cardiac autonomic control: a cross-sectional study. Ann Phys Rehabil Med 2021;64(2):101365. doi: 10.1016/J.REHAB.2020.01.006.
[9] Cousin A, Popielarz S, Wieczorek V, Tiffreau V, Mounier-Vehier C, Thevenon A. Impact of a rehabilitation program on muscular strength and endurance in peripheral arterial occlusive disease patients. Ann Phys Rehabil Med 2011;54:429–42. doi: 10.1016/J.REHAB.2011.07.961.
[10] Guilleron C, Abraham P, Beaune B, Pouliquen C, Henni S, Durand S. Location of ischemia and ischemic pain intensity affect spatiotemporal parameters and leg muscles activity during walking in patients with intermittent claudication. Sci Rep 2021;11:1–9. doi: 10.1038/s41598-021-86351-7.
[11] Gardner AW, Skinner JS, Cantwell BW, Smith LK. Progressive vs single-stage treadmill tests for evaluation of claudication. Med Sci Sports Exerc 1991;23:402–8. doi: 10.1249/00005768-199104000-00003.
[12] Nicolaï SPA, Kruidenier LM, Rouwet E v, Graffius K, Prins MH, Teijink JAW. The walking impairment questionnaire: an effective tool to assess the effect of treatment in patients with intermittent claudication. J Vasc Surg 2009;50:89–94. doi: 10.1016/j.jvs.2008.12.073.
[13] Myers SA, Johanning JM, Stergiou N, Lynch TG, Longo GM, Pipinos II. Claudication distances and the walking impairment questionnaire best describe the ambulatory limitations in patients with symptomatic peripheral arterial disease. J Vasc Surg 2008;47:550–555.e1. doi: 10.1016/j.jvs.2007.10.052.
[14] Enright PL. The six-minute walk test. Respir Care 2003;48:783–5.
[15] Leutzinger TJ, Koutakis P, Fuglestad MA, Rahman H, Despiegelaere H, Hassan M, et al. Peripheral artery disease affects the function of the legs of claudicating patients in a diffuse manner irrespective of the segment of the arterial tree primarily involved. PLoS One 2022;17:e0264598. doi: 10.1371/JOURNAL.PONE.0264598.
[16] McDermott MMG, Ohlmiller SM, Liu K, Guralnik JM, Martin GJ, Pearce WH, et al. Gait alterations associated with walking impairment in people with peripheral arterial disease with and without intermittent claudication. J Am Geriatr Soc 2001;49:747–54. doi: 10.1046/J.1532-5415.2001.49151.X.
[17] Szymczak M, Krupa P, Oszkinis G, Majchrzycki M. Gait pattern in patients with peripheral artery disease. BMC Geriatr 2018;18:1–7. doi: 10.1186/S12877-018-0727-1/TABLES/2.
[18] Guilleron C, Beaune B, Durand S, Pouliquen C, Henni S, Abraham P. Gait alterations in patient with intermittent claudication: effect of unilateral vs bilateral ischemia. Clin Physiol Funct Imaging 2021;41:292–301. doi: 10.1111/CPF.12698.
[19] Gommans LNM, Smid AT, Scheltinga MRM, Cancrinus E, Brooijmans FAM, Meijer K, et al. Prolonged stance phase during walking in intermittent claudication. J Vasc Surg 2017;66:515–22. doi: 10.1016/J.JVS.2017.02.033.
[20] Rahman H, Pipinos II, Johanning JM, Myers SA. Gait variability is affected more by peripheral artery disease than by vascular occlusion. PLoS One 2021;16(3):e0241727. doi: 10.1371/JOURNAL.PONE.0241727.
[21] Myers SA, Pipinos II, Johanning JM, Stergiou N. Gait variability of patients with intermittent claudication is similar before and after the onset of claudication pain. Clin Biomech (Bristol, Avon) 2011;26:729–34. doi: 10.1016/J.CLINBIOMECH.2011.03.005.
[22] Stacy MR, Yu DY, Maxfield MW, Jaba IM, Jozwik BP, Zhuang ZW, et al. Multimodality imaging approach for serial assessment of regional changes in lower extremity arteriogenesis and tissue perfusion in a porcine model of peripheral arterial disease. Circ Cardiovasc Imaging 2014;7:92–9. doi: 10.1161/CIRCIMAGING.113.000884.
[23] 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. J Vasc Surg 2012;55:1654–61. doi: 10.1016/J.JVS.2011.12.060.
[24] Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 1992;326:381–6. doi: 10.1056/NEJM199202063260605.
[25] Newman AB, Siscovick DS, Manolio TA, Polak J, Fried LP, Borhani NO, et al. Ankle-arm index as a marker of atherosclerosis in the cardiovascular health study. Cardiovascular Heart Study (CHS) Collaborative Research Group. Circulation 1993;88:837–45. doi: 10.1161/01.CIR.88.3.837.
[26] Thompson JR, Swanson SA, Haynatzki G, Koutakis P, Johanning JM, Reppert PR, et al. Protein concentration and mitochondrial content in the gastrocnemius predicts mortality rates in patients with peripheral arterial disease. Ann Surg 2015;261:605–10. doi: 10.1097/SLA.0000000000000643.
[27] Edwards AT, Blann AD, Suarez -Mendez VJ, Lardi AM, McCollum CN. Systemic responses in patients with intermittent claudication after treadmill exercise. Br J Surg 1994;81:1738–41. doi: 10.1002/BJS.1800811211.
[28] Hickman P, Harrison DK, Hill A, McLaren M, Tamei H, McCollum PT, et al. Exercise in patients with intermittent claudication results in the generation of oxygen derived free radicals and endothelial damage. Adv Exp Med Biol 1994;361:565–70. doi: 10.1007/978-1-4615-1875-4_96.
[29] Neumann FJ, Waas W, Diehm C, Weiss T, Haupt HM, Zimmermann R, et al. Activation and decreased deformability of neutrophils after intermittent claudication. Circulation 1990;82:922–9. doi: 10.1161/01.CIR.82.3.922.
[30] Drew RC, Blaha CA, Herr MD, Cui R, Sinoway LI. Muscle mechanoreflex activation via passive calf stretch causes renal vasoconstriction in healthy humans. Am J Physiol Regul Integr Comp Physiol 2017;312:R956–64. doi: 10.1152/AJPREGU.00322.2016.
[31] Ross AJ, Gao Z, Luck JC, Blaha CA, Cauffman AE, Aziz F, et al. Coronary exercise hyperemia is impaired in patients with peripheral arterial disease. Ann Vasc Surg 2017;38:260. doi: 10.1016/J.AVSG.2016.05.135.
[32] Muller MD, Drew RC, Cui J, Blaha CA, Mast JL, Sinoway LI. Effect of oxidative stress on sympathetic and renal vascular responses to ischemic exercise. Physiol Rep 2013;1(3):e00047. doi: 10.1002/PHY2.47.
[33] Jin-Kwang Kim D, Kuroki M, Cui J, Gao Z, Carter Luck J, Pai S, et al. Cardiovascular Neurohormonal Regulation: systemic and regional hemodynamic response to activation of the exercise pressor reflex in patients with peripheral artery disease. Am J Physiol Heart Circ Physiol 2020;318:H916. doi: 10.1152/AJPHEART.00493.2019.
[34] Muller MD, Drew RC, Blaha CA, Mast JL, Cui J, Reed AB, et al. Oxidative stress contributes to the augmented exercise pressor reflex in peripheral arterial disease patients. J Physiol 2012;590:6237–46. doi: 10.1113/JPHYSIOL.2012.241281.
[35] Crapo RO, Casaburi R, Coates AL, Enright PL, MacIntyre NR, McKay RT, et al. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111–7. doi: 10.1164/AJRCCM.166.1.AT1102.