Association between daily walking and antioxidant capacity in patients with symptomatic peripheral artery disease

Andrew W. Gardner, PhD,[a] Polly S. Montgomery, MS,[a] Yan D. Zhao, PhD,[b] Federico Silva-Palacios, MD,[c] Zoltan Ungvari, MD, PhD,[a] Anna Csiszar, MD, PhD,[a] *and* William E. Sonntag, PhD,[a] *Oklahoma City, Okla*

ABSTRACT

Objective: The primary aim of the study was to assess whether both the amount and pace of daily walking were associated with circulating antioxidant capacity in symptomatic patients with peripheral artery disease (PAD).

Methods: Community-based walking was measured in 244 men and women who were limited by symptomatic PAD during a 1-week period in which they wore an ankle-mounted step activity monitor. Patients were further characterized by circulating antioxidant capacity with the OxiSelect (Cell Biolabs Inc, San Diego, Calif) hydroxyl radical antioxidant capacity (HORAC) activity assay.

Results: To assess the amount of walking, patients were grouped into low (≤2440 strides/d), middle (2441-3835 strides/d), and high (>3835 strides/d) stride tertiles. HORAC was higher in the middle ($P = .03$) and high ($P = .01$) stride tertiles than in the low tertile, but there was no difference between middle and high tertiles ($P = .44$). To assess the pace of walking, patients were grouped into slow (<25.0 strides/min), middle (25.0-31.6 strides/min), and fast (>31.6 strides/min) cadence tertiles. HORAC was higher in the high cadence tertile than in the low ($P < .01$) and middle ($P < .01$) tertiles, but there was no difference between low and middle tertiles ($P = .48$). Similar findings were obtained on group differences in HORAC after adjusting for age, sex, race, and ankle-brachial index for both the amount and pace of daily walking.

Conclusions: Walking >2440 strides each day and walking at a cadence faster than 31.6 strides/min for 30 minutes each day are both associated with greater circulating antioxidant capacity in symptomatic patients with PAD. The clinical significance is that a home-based walking program may be one approach to increase endogenous antioxidant capacity. (J Vasc Surg 2017;■:1-7.)

Peripheral artery disease (PAD) is a highly prevalent, costly, and deadly condition, particularly in those older than 60 years.[1-3] Furthermore, PAD leads to limitations in patient-perceived health-related quality of life, primarily because of walking dysfunction and leg pain.[4] Consequently, patients with PAD have low daily activity levels, impaired physical function, and faster rates of functional decline and mobility loss over time compared with those without PAD.[5,6]

A possible mechanism for poor walking in older patients with PAD is their chronically high levels of inflammation and oxidative stress, which lead to muscle breakdown and sarcopenia.[7-9] Patients with PAD have higher levels of inflammation than controls do, and inflammation and antioxidant capacity are predictors of exercise performance and microcirculation of the ischemic calf musculature during exercise.[7,10,11] We have reported that circulating inflammatory biomarkers are associated with community-based daily walking in symptomatic patients with PAD, but it is not known whether physical activity modifies circulating antioxidant capacity.[12] It is established that physical activity reduces oxidative stress and increases the ability to respond to oxidative challenges in older adults, suggesting that antioxidant capacity may be increased in older adults who are physically active.[13-16] However, the influence of monitored daily walking on antioxidant capacity in symptomatic patients with PAD, who typically have greater cardiovascular burden and inflammation than healthy older adults do, has not been addressed.[12,17-19]

The primary aim of the study was to assess whether both the amount and pace of daily walking were associated with circulating antioxidant capacity in symptomatic patients with PAD. A secondary aim was to determine whether the daily walking measures were associated with circulating inflammation and with

From the Reynolds Oklahoma Center on Aging, Donald W. Reynolds Department of Geriatric Medicine,[a] Department of Biostatistics and Epidemiology,[b] and Cardiovascular Section, Department of Medicine,[c] University of Oklahoma Health Sciences Center.

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Correspondence: Andrew W. Gardner, PhD, Professor and Vice Chair of Research, Department of Physical Medicine and Rehabilitation, Penn State College of Medicine, 500 University Dr, PO Box 850, Mail Code R120, Hershey, PA 17033 (e-mail: agardner4@hmc.psu.edu).

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endothelial cell inflammation, oxidative stress, and apoptosis. Our primary hypothesis was that more daily strides and faster cadence would be associated with increased levels of circulating antioxidant capacity.

METHODS

Patients

Approval and informed consent. The Institutional Review Board at the University of Oklahoma Health Sciences Center approved the procedures of this study. Written informed consent was obtained from each patient at the beginning of investigation.

Recruitment. Patients who were not currently exercising were recruited from vascular laboratories and vascular clinics from the University of Oklahoma Health Sciences Center for possible enrollment into an exercise rehabilitation program to treat leg pain secondary to PAD.

Baseline clinical characteristics obtained from a medical history and physical examination. Patients were evaluated in the morning at the Clinical Research Center at the University of Oklahoma Health Sciences Center. Patients arrived fasted but were permitted to take their usual medications. To begin the study visit, patients were evaluated with a medical history and physical examination in which demographic information, height, weight, waist circumference, cardiovascular risk factors, comorbid conditions, claudication history, ankle-brachial index (ABI), and a list of current medications were obtained. Following the medical history and physical examination, nursing personnel obtained blood samples, and exercise personnel performed the exercise tests. The nursing and exercise personnel were blinded to the results from the medical history and physical examination.

Inclusion and exclusion criteria. Patients who were limited by symptomatic PAD were included in this study if they met the following criteria: history of ambulatory leg pain, ambulatory leg pain confirmed by treadmill exercise, and ABI ≤0.90 at rest or ≤0.73 after exercise.[4,20,21] Patients were excluded for the following conditions: absence of PAD (ABI >0.90 at rest and ABI >0.73 after exercise), noncompressible vessels (ABI ≥1.40), asymptomatic PAD, use of medications indicated for the treatment of claudication (cilostazol or pentoxifylline) initiated within 3 months before investigation, exercise limited by other diseases or conditions, active cancer, end-stage renal disease (defined as stage 5 chronic kidney disease), and abnormal liver function.

Measurements

Claudication onset time (COT) and peak walking time (PWT) obtained from a graded maximal treadmill test. Patients completed a graded treadmill test to determine study eligibility and then repeated the test on a following visit within 1 week to obtain the outcome measures of COT and PWT.[4,22] Using our procedures, the test-retest intraclass reliability coefficient is $R = .89$ for COT and $R = .93$ for PWT.[4]

Total walk distance obtained from a 6-minute walk test. Patients performed an over-ground 6-minute walk test supervised by trained exercise technicians.[23] The total distance walked during the test was recorded. The test-retest intraclass reliability coefficient is $R = .94$ for total 6-minute walking distance.[23]

Daily walking obtained from a step activity monitor. Daily walking was measured using a step activity monitor (StepWatch3; Ortho Innovations, Oklahoma City, Okla).[24] Walking was measured during a consecutive 7 days in which patients were instructed to wear the monitor during waking hours and to remove it before retiring to bed and while showering. The step activity monitor was attached to the right ankle above the lateral malleolus by an elastic Velcro strap and continuously recorded the number of strides taken each day and the number of minutes spent walking each day. The daily number of strides and walking time are further analyzed by the software program to determine the peak activity index, obtained by ranking all minutes of the day according to cadence, then taking the average of the highest 30 values. The outcome measures are recorded for each day, and then the daily averages are averaged over the 7-day monitoring period. The accuracy of the step activity monitor exceeds 99% ± 1% in patients with claudication, and the test-retest intraclass reliability coefficient for the daily ambulatory activity measures ranges from $R = .83$ to $R = .94$.[24]

Blood sampling. Approximately 10 mL of blood was drawn by venipuncture from an antecubital vein once at baseline, collected in Vacutainers (Becton Dickinson, Franklin Lakes, NJ), and distributed in 0.5-mL aliquots. The samples were stored at −80°C and subsequently batched for analysis.

Serum antioxidant capacity. Hydroxyl radical antioxidant capacity (HORAC) was measured from sera using the OxiSelect (Cell Biolabs Inc, San Diego, Calif) HORAC activity assay to determine the capacity of antioxidant

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center prospective cohort study.
- **Take Home Message:** Study participants who walked more and at a greater pace demonstrated greater hydroxyl radical antioxidant capacity and lower concentrations of high-sensitivity C-reactive protein.
- **Recommendation:** The authors suggest that home-based walking programs may increase endogenous antioxidant capacity; still to be proven is the association between increased oxidative stress and poor walking capacity.