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Lower Extremity Nerve Function in Patients With Lower Extremity Ischemia

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Abstract

Background—We determined whether lower extremity ischemia, as measured by the ankle brachial index (ABI), is associated with impaired lower extremity nerve function.

Methods—Participants included 478 persons with peripheral arterial disease (PAD) identified from noninvasive vascular laboratories and 292 persons without PAD identified from a general medicine practice and noninvasive vascular laboratories. Peripheral arterial disease was defined as an ABI lower than 0.90 (mild PAD: ABI, 0.70 to <0.90; moderate PAD: ABI, 0.50 to <0.70; and severe PAD: ABI, <0.50). The ABI and electrophysiologic measures of the peroneal, sural, and ulnar nerves were obtained.

Results—Among 546 participants without diabetes, PAD participants had significantly impaired peripheral nerve function in the upper and lower extremities compared with non-PAD participants. After adjusting for age, sex, race, smoking, height, body mass index, recruitment source, alcohol use, disk disease, spinal stenosis, cardiac disease, and cerebrovascular disease, these associations were not statistically significant. After adjusting for confounders among nondiabetic participants, those with severe PAD (ABI, <0.50) had poorer peroneal nerve conduction velocity (NCV) compared with participants without PAD (42.6 vs 44.8 m/s; *P*=.003) and poorer peroneal NCV compared with participants with mild PAD (42.6 vs 45.0 m/s; *P*=.001) or moderate PAD (42.6 vs 44.1 m/s; *P*=.03). Among 224 participants with diabetes, after adjusting for confounders, PAD was associated with poorer peroneal NCV (40.8 vs 43.5 m/s; *P*=.01), sural nerve amplitude (3.1 vs 4.8 μV; *P*=.045), and ulnar NCV (47.6 vs 50.2 m/s; *P*=.03) compared with those without PAD.

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Conclusions—Our findings suggest that leg ischemia impairs peroneal nerve function. This association is less strong in patients with diabetes, perhaps because of the overriding influence of diabetes on peripheral nerve function. Clinicians should consider screening for PAD in patients with idiopathic peroneal nerve dysfunction. Peripheral arterial disease–associated nerve dysfunction may contribute to PAD-associated functional impairment.

Lower extremity peripheral arterial disease (PAD) affects 8 million men and women in the United States.[1] Previous studies have identified impaired lower extremity nerve function in patients with PAD with severe, limb-threatening ischemia.[2,3] However, most patients with PAD do not develop limb-threatening ischemia. Associations between chronic leg ischemia that is not limb threatening and peripheral nerve function are unclear.[4]

The blood supply of lower extremity nerves is potentially affected by PAD. The lumbosacral nerve plexus is supplied by the inferior gluteal artery, and a branch of the popliteal artery supplies the common peroneal nerve. Thus, noncritical lower extremity ischemia may potentially affect lower extremity nerve function. If lower extremity ischemia is associated with peripheral neuropathy, this finding has potential implications for the diagnosis and treatment of peripheral neuropathy. Approximately 15% of Americans 40 years and older have peripheral neuropathy.[5] As many as one third may have idiopathic neuropathy.[6] Peripheral neuropathy causes lower extremity numbness and pain and may contribute to disability.[7] If lower extremity ischemia is associated with impaired lower extremity nerve function, ischemia-associated neuropathy may contribute to the functional impairment and functional decline observed in patients with PAD.[8,9]

To determine associations between noncritical lower extremity ischemia and lower extremity neuropathy, we studied relationships between the ankle brachial index (ABI) and peripheral nerve function among 770 men and women with and without PAD. We hypothesized that lower ABI levels would be associated with greater impairment in lower extremity nerve function. Because diabetes mellitus is known to be associated with neuropathy, analyses were performed separately among participants with and without diabetes. To determine whether the effects of lower extremity ischemia are specific to lower extremity nerve function, we also studied associations between ABI levels and upper extremity nerve function.

METHODS

PARTICIPANT IDENTIFICATION

The protocol was approved by the institutional review boards of Northwestern University Feinberg School of Medicine and Catholic Health Partners Hospitals, Chicago, Ill. Participants gave informed consent. Participants included 368 persons attending their fourth annual follow-up visit in the Walking and Leg Circulation Study (WALCS)[1,2] and 402 individuals newly identified for the present study (WALCS II). Participants were 59 years and older. The PAD participants were identified consecutively from among patients diagnosed with PAD in 3 Chicago-area noninvasive vascular laboratories. Non-PAD participants were identified consecutively from patients with appointments in a large general medicine practice at Northwestern University and from among consecutive patients with normal findings from lower extremity arterial studies in the 3 vascular laboratories. Patients with a normal ABI who had a history of lower extremity revascularization or a previous ABI lower than 0.90 during participation in the WALCS cohort were not included. Our cohort included more PAD than non-PAD participants to meet sample size calculations for WALCS II longitudinal aims, which are beyond the scope of this article. There was no matching of characteristics between PAD and non-PAD participants.

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EXCLUSION CRITERIA

Peripheral arterial disease was defined as an ABI lower than 0.90.[8–10] Absence of PAD was defined as an ABI of 0.90 or higher and 1.30 or lower.[11] An ABI lower than 0.90 is 80% sensitive and 96% specific for angiographically diagnosed PAD.[12] Individuals with an ABI higher than 1.30 were excluded because this indicates poorly compressible leg arteries and inability to gauge arterial perfusion accurately.[11,13]

Patients with dementia were excluded because of their inability to answer questions accurately. Nursing home residents, wheelchair-bound patients, and patients with foot or leg amputations were excluded because they have severely impaired functioning. Non-English–speaking patients were excluded because investigators were not fluent in non-English languages. Patients with recent major surgery were also excluded.

ABI MEASUREMENT AND LEG SYMPTOMS

The ABI was measured using established methods.[8,9] After participants rested supine for 5 minutes, a handheld Doppler probe (Pocket Dop II; Nicolet Vascular, Golden, Colo) was used to measure systolic pressures in the right brachial, dorsalis pedis, and posterior tibial arteries and the left dorsalis pedis, posterior tibial, and brachial arteries. Each pressure was measured twice.[8,9] The ABI was calculated in each leg by dividing average pressures in each leg by the average of the 4 brachial pressures.[1,2] Average brachial pressures in the arm with the highest pressure were used when one brachial pressure was higher than the opposite brachial pressure in both measurement sets and the 2 brachial pressures differed by 10 mm Hg or more in at least 1 measurement set because in such cases subclavian stenosis was possible.[8,9,14] The lowest leg ABI was used in analyses.

We used the San Diego claudication questionnaire to measure the presence and type of leg symptoms based on previous studies.[8,15]

PERIPHERAL NERVE FUNCTION

Electroneurography is considered the gold standard for measurement of peripheral nerve function and has been previously validated for measuring both sensory and motor peripheral nerve function.[16–18] A previous study showed that the coefficient of variability of sensory and motor nerve conduction velocity (NCV) was 2.2% to 6.7%.[19] In another study, correlation coefficients between nerve conduction studies performed twice during 1 week in 20 patients with diabetes were higher than 0.90 for sensory amplitude of ulnar, median, and sural nerves.[20]

Nerve function was measured in both legs by the electrodiagnostic supervisor at Northwestern Memorial Hospital. The technician, certified by the American Association of Electrodiagnostic Technologists, has 30 years of experience in electrodiagnostic testing. The technician was blinded to the participants' history, including presence of diabetes or PAD. Results for the leg with the lowest ABI were used in analyses comparing nerve function between individuals. We selected the peroneal and sural nerves for study because their length increases their susceptibility to arterial obstruction at multiple locations in the lower extremities. The peroneal and sural nerves allowed us to measure both motor and sensory peripheral nerve function. Ulnar motor NCV in 1 randomly selected upper extremity was also measured. The testing room was maintained at 25°C or higher. Surface skin temperature was recorded.

Peroneal NCV (Lower Extremity Motor Nerve Testing)—Surface recording electrodes were placed on the dorsum of the foot, over the belly of the extensor digitorum brevis. Two stimulating bipolar electrodes were placed over the peroneal nerve. The first electrode was placed over the anterior surface of the ankle, 7 cm from the recording electrode. The second

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electrode was placed behind the knee. A ground electrode was positioned between the recording and stimulating electrodes. A mild electrical impulse was applied that progressively increased until the maximum amplitude was obtained. The time required for electrical impulses to travel from the ankle to the recording electrode (t1) and from the electrode at the fibular head to the recording electrode (t2) were recorded along with the distance between the 2 pairs of electrodes (distance) and the amplitude of the sinusoids (a1 and a2). The NCV was calculated as distance/(t2−t1). Peroneal amplitude was measured from baseline to the negative peak. Peroneal latency was recorded.

Sural Nerve Testing (Lower Extremity Sensory Nerve)—An active recording electrode was placed behind the lateral malleolus. A reference electrode was placed 2 cm distally. By convention, the sural nerve was stimulated 14 cm proximal to the recording electrode, over the posterolateral calf. Sural amplitude and latency were recorded. Sural NCV was calculated from latency data and the distance between the stimulating and recording electrodes.

Ulnar NCV (Upper Extremity Motor Nerve)—The active electrode was placed over the abductor digiti minimi muscle. The reference electrode was placed at the base of the fifth digit. A ground electrode was placed over the dorsum of the hand. The ulnar nerve was stimulated at the wrist and above the elbow. The distance between the 2 stimulation points and the time required for electrical stimulation to travel between these 2 points were used to calculate ulnar motor NCV.

COMORBIDITIES

Algorithms developed for the Women's Health and Aging Study were used to document comorbidities.[21] These algorithms combine data from patient report, physical examination, medical record review, medications, laboratory values, and a primary care physician questionnaire. The comorbidities assessed were diabetes mellitus, angina, myocardial infarction, stroke, heart failure, spinal stenosis, and disk disease. Participants could be classified as having diabetes if they met 1 or more of the following criteria: (1) use of insulin or an oral hypoglycemic agent; (2) the participant's physician reported presence of diabetes mellitus; (3) the participant reported physician-diagnosed diabetes mellitus; and (4) a hemoglobin A_{1c} level of 10% or higher was identified during medical record review. Participants were classified with spinal stenosis or disk disease if they met 1 or more of the following criteria: documented prior surgery for spinal stenosis (or disk disease), documented hospitalization for spinal stenosis (or disk disease), physician-reported history of spinal stenosis (or disk disease), or current treatment for spinal stenosis (or disk disease). An additional criterion for spinal stenosis was exertional leg symptoms relieved by rest in a patient with a normal ABI.

OTHER MEASURES

Height and weight were measured at the study visit. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.[2] Cigarette smoking history and alcohol consumption were based on self-report. History of lower extremity revascularization was determined based on participant report and confirmed by medical record review or the primary care physician questionnaire.

STATISTICAL ANALYSES

Differences in continuous variables between participants with vs without PAD were evaluated using analyses of variance. Rates for dichotomous variables were compared using χ^2 tests. Because diabetes mellitus is known to impair nerve function and to be an important risk factor

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for PAD, all analyses were performed separately among subsets of participants with and without diabetes mellitus. Within groups of PAD participants with and without diabetes mellitus, differences in nerve function across ABI categories were evaluated using multiple linear regression analyses, adjusting for age, race, sex, cigarette smoking, BMI, height, recruitment cohort (WALCS vs WALCS II), alcohol use, and co-morbidities likely to confound the association with nerve functioning (disk disease, spinal stenosis, and cardiovascular diseases). For NCV and latency analyses, participants with no response to stimulation were excluded from analyses. The significance of between-group comparisons in dichotomous variable rates was based on logistic regression using dummy variables for ABI categories. Among nondiabetic PAD participants whose right and left leg ABIs differed by 0.20 or higher and lower than 0.20, respectively, differences in lower extremity nerve function were compared between legs with the highest vs lowest ABI levels of the same participant using paired *t* tests. Analyses were performed using SAS Statistical Software (SAS Inc, Cary, NC). $P<.05$ was considered statistically significant.

RESULTS

Table 1 gives the characteristics of the study population. The prevalence of diabetes among PAD participants was comparable to that of other studies.[22–24] Compared with participants without PAD, persons with PAD had lower BMI, a greater number of pack-years of smoking, more cardiac or cerebrovascular diseases, and a lower prevalence of spinal stenosis (Table 1). Among nondiabetic participants, those with PAD were older and included a higher prevalence of men compared with those without PAD. Nondiabetic PAD participants had reduced leg skin temperature compared with nondiabetic participants without PAD (Table 1). There were no differences in upper extremity skin temperature between PAD and non-PAD participants. There were no significant differences in upper or lower extremity nerve function among persons with vs without spinal stenosis or disk disease (data not shown).

NERVE FUNCTION

Diabetic vs Nondiabetic Participants—Table 2 gives the associations between presence vs absence of diabetes mellitus and nerve function within the entire cohort, adjusting for age, sex, race, BMI, smoking, comorbidities, recruitment cohort, height, alcohol consumption, lower extremity revascularization, and ABI. Participants with diabetes had poorer performance in all measures of nerve function compared with those without diabetes.

PAD vs Non-PAD Participants Without Diabetes—In unadjusted analyses of participants without diabetes mellitus, PAD participants had poorer performance in most nerve outcomes compared with participants without PAD (Table 3). After adjusting for confounders, there were no significant differences in lower or upper extremity nerve function between PAD vs non-PAD participants without diabetes (Table 3).

PAD vs Non-PAD Participants With Diabetes—Among participants with diabetes mellitus, PAD participants had lower peroneal NCV, sural nerve amplitude, and ulnar NCV compared with participants without PAD, after adjusting for confounders (Table 3). Results for participants with diabetes did not substantially change after additional adjustment for the number of diabetes medications taken (data not shown). The results listed in Table 3 did not change substantially after additional adjustment for limb temperature (data not shown).

INTERACTION BETWEEN DIABETES AND PAD ON NERVE FUNCTION

In tests for interactions between diabetes and PAD on nerve function, significant interactions were observed for diabetes and PAD on ulnar NCV ($P=.04$) and ulnar sensory latency ($P=.007$). No other significant interactions were observed.

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SEVERE ISCHEMIA IS ASSOCIATED WITH REDUCED PERONEAL NERVE FUNCTION IN NONDIABETIC PARTICIPANTS

Table 4 gives nerve function by ABI category among PAD participants, fully adjusting for confounders. Among nondiabetic participants with an ABI lower than 0.90, lower ABI values were associated with lower peroneal NCV and lower peroneal amplitude (Table 4). Among nondiabetic participants, those with severe PAD (ABI, <0.50) had lower peroneal NCV compared with participants with moderate PAD (ABI, 0.50 to <0.70) (P = .03) and participants with mild PAD (ABI, 0.70 to <0.90) (P=.001). In separate fully adjusted analyses including both PAD and non-PAD participants, participants with an ABI lower than 0.50 had significantly poorer peroneal NCV compared with participants without PAD (ABI, 0.90 to 1.30) (42.6 vs 44.8 m/s, P=.003). The results given in Table 4 did not change substantially after additional adjustment for limb temperature (data not shown).

NERVE FUNCTION IN PAD PARTICIPANTS WITH DISCREPANCIES IN THE RIGHT VS LEFT LEG ABI

Nerve function was compared between legs with higher vs lower ABI levels among nondiabetic PAD participants with differences in ABI of 0.20 or higher between the right and left legs. The leg with lower ABI had slower peroneal NCV and lower peroneal nerve amplitude compared with the higher leg ABI (Table 5). Among nondiabetic PAD participants whose left and right leg ABI values differed by less than 0.20, there were no differences in nerve function between the leg with the higher vs lower ABI (data not shown).

COMMENT

Previous studies have been inconclusive regarding associations between chronic lower extremity ischemia and lower extremity nerve function.[25–27] Among 546 nondiabetic participants, those with severe leg ischemia (ABI, <0.50) had significantly poorer peroneal nerve function compared with participants with no PAD, mild PAD (ABI 0.70 to <0.90), or moderate PAD (ABI, 0.50 to <0.70). Among nondiabetic PAD participants with left vs right leg ABI discrepancies of 0.20 or greater, peroneal NCV and amplitude were significantly lower in the leg with lower ABI. These latter data provide additional evidence for a direct detrimental effect of lower extremity ischemia on peroneal nerve function, since the potential problem of incomplete adjustment for confounding variables should be eliminated by comparing legs in the same participant. These findings support the hypothesis that severe lower extremity ischemia exerts a direct negative effect on peroneal nerve function among nondiabetic men and women.

We observed no significant associations between ABI and sural or ulnar nerve function in nondiabetic participants. The absence of association between ABI and ulnar nerve function was anticipated because the ABI does not reflect blood supply to the upper extremities. It is unclear why there was not an association between the ABI and sural nerve function. One possibility is that the sural nerve benefits from collateral blood supply to a greater degree compared with the peroneal nerve.

Among diabetic participants, our findings showing poorer nerve function in both lower and upper extremities among PAD compared with non-PAD participants argue against a direct adverse effect of lower extremity ischemia on lower extremity nerve function in persons with diabetes. Among diabetic participants, the lack of association between severe ischemia (ABI, <0.50) and reduced lower extremity nerve function also suggests that lower extremity ischemia does not exert a clinically meaningful effect on lower extremity nerve function among the patients with diabetes. The adverse effects of diabetes may override adverse effects of lower extremity ischemia on nerve function.

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Prior studies regarding PAD and lower extremity nerve function have been conflicting.[25–27] Chopra and Hurwitz[25,26] studied nerve conduction in the median, ulnar, peroneal, and femoral nerves in persons with and without PAD. Compared with non-PAD participants, only the median sensory nerve amplitude was slightly reduced in the PAD participants.[25,26] Weber and Ziegler[27] performed electrodiagnostic testing of the peroneal, posterior tibial, and sural nerves in 44 participants with PAD (7 legs with pain at rest and 37 legs with intermittent claudication) and 37 participants without PAD. Peroneal and tibial nerve function, but not sural nerve function, were lower in the legs with PAD and intermittent claudication compared with the controls.[27] The most severe findings were observed in the legs of PAD patients with pain at rest. Finally, Teunissen et al[28] compared median, tibial, and sural nerve function between 97 nondiabetic patients with PAD and 96 nondiabetic controls, matched by age and sex. Median nerve motor NCV, tibial nerve motor NCV, minimal F-wave and M-wave latencies of the median nerve, and sural nerve amplitude were worse in PAD patients than in controls. However, there were no differences in median motor nerve latency or action potential, median sensory NCV or amplitude, tibial nerve latency, tibial nerve action potential, tibial minimal F-wave and M-wave latencies, or sural NCV between participants with vs without PAD. The study by Teunissen et al[28] is limited by lack of statistical adjustment for differences in atherosclerotic risk factors and other potential confounders between the PAD and control participants.

Many prior studies of PAD and lower extremity nerve function have included small numbers of participants and have not statistically adjusted for potential confounders. This latter characteristic is important because the data reported herein showed that adjustment for confounders eliminated all significant differences in nerve function between nondiabetic participants with vs without PAD. To our knowledge, our study is the largest to compare electrodiagnostic testing results between patients with noncritical lower extremity ischemia and those without PAD, and no other studies have assessed associations between nerve function and the ABI among PAD participants.

Our study has limitations. First, the associations reported herein between lower ABI levels and greater impairment in nerve function cannot be concluded as causal. Evidence supporting causality includes substantiation of temporality, biological plausibility, consistency of findings, evidence for dose response (ie, in this case more severe ischemia being associated with more severe deficits in nerve function), coherence of data, and strength of the association. Only some of this evidence is available from the present study. Second, we did not collect fasting glucose levels. Some nondiabetic participants may have been misclassified with regard to their diabetes status. Third, non-PAD participants were recruited from Chicago medical centers and may have had more comorbid illnesses compared with typical age-matched Chicagoans outside of medical centers. This characteristic of our control population may have affected comparisons between the PAD and non-PAD populations. Fourth, we did not collect data on the anatomic location of lower extremity arterial obstruction.

Our data are consistent with the hypothesis that severe lower extremity arterial ischemia in patients without critical limb ischemia contributes to impaired peroneal nerve function in older men and women. Clinicians should consider screening for PAD in patients with idiopathic peroneal nerve dysfunction. Further study is needed to determine whether poorer peripheral nerve function in persons with PAD contributes to PAD-associated functional impairment. If peripheral neuropathy is part of the causal pathway between PAD and disability, then peripheral neuropathy may be a new potential treatment target for persons with PAD.

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References

1. American Heart Association. Heart Disease and Stroke Statistics—2006 Update. Dallas, Tex: American Heart Association; 2006.
2. Kumlin T, Seppalainen AM, Railo J. Electroneurolography in intermittent claudication due to obliterative arteriosclerosis. Angiology 1974;25:373–380. [PubMed: 4367194]
3. Eames RA, Lange LS. Clinical and pathological study of ischaemic neuropathy. J Neurol Neurosurg Psychiatry 1967;30:215–226. [PubMed: 6033616]
4. England JD, Regensteiner JG, Ringel SP, Carry MR, Hiatt WR. Muscle denervation in peripheral arterial disease. Neurology 1992;42:994–999. [PubMed: 1579257]
5. Gregg EW, Sorlie P, Paulose-Ram R, et al. Prevalence of lower-extremity disease in the US adult population >40 years of age with and without diabetes. Diabetes Care 2004;27:1591–1597. [PubMed: 15220233]
6. Gordon Smith A, Robinson Singleton R. Idiopathic neuropathy, prediabetes, and the metabolic syndrome. J Neurol Sci 2006;242:9–14. [PubMed: 16448668]
7. Resnick HE, Stansberry KB, Harris TB, et al. Diabetes, peripheral neuropathy, and old age disability. Muscle Nerve 2002;25:43–50. [PubMed: 11754184]
8. McDermott MM, Greenland P, Liu K, et al. Leg symptoms commonly reported by men and women with lower extremity peripheral arterial disease: associated clinical characteristics and functional impairment. JAMA 2001;286:1599–1606. [PubMed: 11585483]
9. McDermott MM, Liu K, Greenland P, et al. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. JAMA 2004;292:453–461. [PubMed: 15280343]
10. Newman AB, Siscovick DS, Manolio TA, et al. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Circulation 1993;88:837–845. [PubMed: 8353913]
11. Resnick HE, Lindsay RS, McDermott MM, et al. Relationship of high and low ankle brachial index to all-cause and cardiovascular mortality: the Strong Heart Study. Circulation 2004;109:733–739. [PubMed: 14970108]
12. Lijmer JG, Hunink MG, van den Dungen JJ, Loonstra J, Smit AJ. ROC analysis of noninvasive tests for peripheral arterial disease. Ultrasound Med Biol 1996;22:391–398. [PubMed: 8795165]
13. Wang JC, Criqui MH, Denenberg JO, McDermott MM, Golomb BA, Fronek A. Exertional leg pain in patients with and without peripheral arterial disease. Circulation 2005;112:3501–3508. [PubMed: 16316971]
14. Hiatt WR, Hoag S, Hamman RF. Effect of diagnostic criteria on the prevalence of peripheral arterial disease: the San Luis Valley Diabetes Study. Circulation 1995;91:1472–1479. [PubMed: 7867189]
15. Criqui MH, Denenberg JO, Bird CE, Fronek A, Klauber MR, Langer RD. The correlation between symptoms and non-invasive test results in patients referred for peripheral arterial disease testing. Vasc Med 1996;1:65–71. [PubMed: 9546918]
16. Magladery JW, McDougal DB Jr. Electrophysiological studies of nerve and reflex activity in normal man, I: identification of certain reflexes in the electromyogram and the conduction velocity of peripheral nerve fibres. Bull Johns Hopkins Hosp 1950;86:265–290. [PubMed: 15414383]
17. Lambert EH. Diagnostic value of electrical stimulation of motor nerves. Electroencephalogr Clin Neurophysiol Suppl 1962;22(suppl):9–16.
18. Gilliatt RW, Sears TW. Sensory nerve action potentials in patients with peripheral nerve lesions. J Neurol Neurosurg Psychiatry 1958;21:109–118. [PubMed: 13539652]
19. Bleasel AF, Tuck RR. Variability of repeated nerve conduction studies. Electroencephalogr Clin Neurophysiol 1991;81:417–420. [PubMed: 1721581]

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20. Dyck PJ, Kratz KM, Lehman KA, et al. The Rochester Diabetic Neuropathy Study: design, criteria for types of neuropathy, selection bias, and reproducibility of neuropathic tests. Neurology 1991;41:799–807. [PubMed: 2046920]

21. Guralnik, JM.; Fried, LP.; Simonsick, EM., et al. The Women's Health and Aging Study: Health and Social Characteristics of Older Women With Disability. Bethesda, Md: National Institute on Aging; 1995:appendix E; NIH publication 95–4009

22. Aquino R, Johnnides C, Makaroun M, et al. Natural history of claudication: long-term serial follow-up study of 1,244 claudicants. J Vasc Surg 2001;34:962–970. [PubMed: 11743546]

23. Feinglass J, McCarthy WJ, Slavensky R, Manheim LM, Martin GJ. Effect of lower extremity blood pressure on physical functioning in patients who have intermittent claudication. J Vasc Surg 1996;24:503–512. [PubMed: 8911399]

24. Gardner AW, Montgomery PS, Killewich LA. Natural history of physical function in older men with intermittent claudication. J Vasc Surg 2004;40:73–78. [PubMed: 15218465]

25. Chopra JS, Hurwitz LJ. Femoral nerve conduction in diabetes and chronic occlusive vascular disease. J Neurol Neurosurg Psychiatry 1968;31:28–33. [PubMed: 5644929]

26. Chopra JS, Hurwitz LJ. A comparative study of peripheral nerve conduction in diabetes and nondiabetic chronic occlusive vascular disease. Brain 1969;92:83–96. [PubMed: 4304425]

27. Weber F, Ziegler A. Axonal neuropathy in chronic peripheral arterial occlusive disease. Muscle Nerve 2002;26:471–476. [PubMed: 12362411]

28. Teunissen LL, Franssen H, Wokke JHJ, et al. Is cardiovascular disease a risk factor in the development of axonal polyneuropathy? J Neurol Neurosurg Psychiatry 2002;72:590–595. [PubMed: 11971043]

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Table 1

Characteristics of 770 Participants With and Without PAD According to Presence vs Absence of Diabetes at Baseline*

Characteristic	All Participants (N = 770)	No Diabetes Mellitus			Diabetes Mellitus		
		No PAD (n = 225)	PAD (n = 321)	*P* Value	No PAD (n = 67)	PAD (n = 157)	*P* Value
Age, y	73.8 (8.2)	71.7 (7.8)	76.0 (8.2)	<.001	71.6 (7.8)	73.2 (8.1)	.18
Male	49.4	40.4	49.8	.03	50.8	60.9	.16
African American race	18.4	16.4	13.4	.32	35.8	24.2	.08
Ankle brachial index	0.80 (0.26)	1.09 (0.09)	0.63 (0.16)	<.001	1.08 (0.10)	0.62 (0.16)	<.001
Cigarette smoking (pack-years)	28.4 (34.0)	15.1 (25.0)	37.8 (36.2)	<.001	21.2 (26.9)	31.1 (36.8)	.049
BMI	28.4 (5.5)	28.1 (5.3)	26.7 (4.4)	.002	32.8 (7.0)	30.3 (5.5)	.006
Mean No. of cardiac or cerebrovascular diseases	0.93 (1.11)	0.51 (0.85)	0.94 (1.11)	<.001	0.88 (0.84)	1.52 (1.26	<.001
No. of alcoholic drinks per week	3.3 (6.0)	3.8 (5.7)	3.8 (6.4)	.96	1.5 (2.9)	2.6 (6.2)	.17
Lower extremity temperature, °C	31.9 (1.3)	32.1 (1.4)	31.8 (1.3)	.02	32.1 (1.2)	31.8 (1.2)	.12
Upper extremity temperature, °C	33.0 (1.1)	33.0 (1.1)	33.0 (1.1)	.89	32.9 (1.1)	32.9 (1.1)	.99
Hypertension	44.8	39.1	45.2	.16	46.3	51.6	.47
Knee arthritis	15.6	16.9	13.1	.22	26.9	14.0	.02
History of cancer	21.3	22.2	22.1	.98	22.4	17.8	.43
History of angina	29.5	16.7	30.5	<.001	32.8	44.2	.11
History of myocardial infarction	22.1	15.6	21.9	.07	13.4	35.7	.001
History of heart failure	24.8	12.4	23.7	.001	25.4	44.6	.007
Spinal stenosis or disk disease	50.5	58.7	43.9	.001	64.2	46.5	.02
Leg symptoms							
Classic symptoms of intermittent claudication	16.0	7.2	20.4	<.001	13.4	20.7	<.001
No pain	36.4	61.0	25.4		43.3	20.7	
Any exertional leg pain	63.9	39.6	74.8	<.001	56.7	79.6	<.001
Lower extremity revascularization	20.1	0	31.2	<.001	0	35.0	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); PAD, peripheral arterial disease.

*Data are given as mean (SD) or percentage unless otherwise specified.

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Table 2

Adjusted Associations Between Presence vs Absence of Diabetes and Nerve Function Among Men and Women With and Without Peripheral Arterial Disease*

Nerve Function	No Diabetes Mellitus (n = 546)	Diabetes Mellitus (n = 224)	*P* Value
Peroneal NCV, m/s	44.0 (0.23)	41.6 (0.37)	<.001
Peroneal nerve amplitude, μV	3.4 (0.16)	2.2 (0.24)	<.001
Peroneal nerve latency, ms	4.8 (0.05)	5.2 (0.08)	<.001
Sural nerve NCV, m/s	43.4 (0.43)	41.8 (0.78)	.08
Sural nerve amplitude, μV	5.9 (0.26)	3.9 (0.40)	<.001
Sural nerve latency, ms	3.4 (0.18)	4.2 (0.33)	.03
Ulnar NCV, m/s	52.2 (0.27)	48.8 (0.42)	<.001
Ulnar sensory amplitude, μV	18.4 (0.50)	15.8 (0.77)	.006
Ulnar sensory latency, ms	2.7 (0.02)	2.9 (0.03)	<.001

Abbreviation: NCV, nerve conduction velocity.

*Data are given as mean (SE) unless otherwise specified. Analyses are adjusted for age, sex, body mass index, race, cigarette smoking, comorbidities, recruitment cohort, height, alcohol consumption, lower extremity revascularization history, and ankle brachial index categories. Participants with no response to stimulation were excluded from analyses for latency and NCV. Zero values for NCV and latency have been excluded from analyses.

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Table 3

Nerve Function According to Presence vs Absence of PAD Among 770 Participants With and Without Diabetes Mellitus

	No Diabetes Mellitus			Diabetes Mellitus		
Nerve Function	**No PAD (n = 225)**	**PAD (n = 321)**	***P* Value**	**No PAD (n = 67)**	**PAD (n = 157)**	***P* Value**
		Unadjusted Analyses*				
Peroneal NCV, m/s	45.2 (4.6)	43.8 (4.8)	.002	43.0 (5.6)	41.1 (5.5)	.04
Peroneal nerve amplitude, μV	3.95 (4.68)	3.14 (2.26)	.01	2.69 (2.22)	2.11 (2.15)	.08
Peroneal nerve latency, ms	4.62 (0.77)	4.84 (0.80)	.003	4.99 (1.49)	5.19 (1.44)	.41
Sural nerve NCV, m/s	45.1 (6.8)	42.2 (6.9)	<.001	44.4 (9.1)	42.0 (9.2)	.21
Sural nerve amplitude, μV	6.77 (5.53)	5.65 (5.91)	.03	4.03 (4.76)	3.50 (4.85)	.48
Sural nerve latency, ms	3.17 (0.49)	3.47 (1.26)	.005	3.36 (1.18)	4.31 (7.53)	.47
Ulnar NCV, m/s	53.1 (5.75)	52.1 (5.02)	.04	50.0 (5.65)	47.8 (7.40)	.04
Ulnar sensory amplitude, μV	20.9 (12.5)	17.7 (10.9)	.002	15.0 (10.5)	13.5 (12.4)	.40
Ulnar sensory latency, ms	2.68 (0.47)	2.72 (0.27)	.31	2.84 (0.35)	3.02 (0.63)	.04
		Adjusted Analyses†				
Peroneal NCV, m/s	44.7 (0.34)	44.2 (0.28)	.28	43.5 (0.77)	40.8 (0.50)	.01
Peroneal nerve amplitude, μV	3.8 (0.28)	3.3 (0.22)	.20	2.7 (0.32)	2.1 (0.20)	.14
Peroneal nerve latency, ms	4.7 (0.06)	4.8 (0.05)	.29	4.9 (0.23)	5.2 (0.15)	.32
Sural nerve NCV, m/s	44.2 (0.61)	42.9 (0.51)	.14	45.5 (1.92)	41.3 (1.23)	.11
Sural nerve amplitude, μV	6.2 (0.44)	6.0 (0.35)	.75	4.8 (0.63)	3.1 (0.39)	.045
Sural nerve latency, ms	3.3 (0.09)	3.4 (0.08)	.39	2.4 (1.39)	4.8 (0.89)	.21
Ulnar NCV, m/s	52.5 (0.40)	52.4 (0.32)	.95	50.2 (0.91)	47.6 (0.56)	.03
Ulnar sensory amplitude, μV	18.9 (0.79)	19.0 (0.63)	.92	15.1 (1.56)	13.6 (0.96)	.46
Ulnar sensory latency, ms	2.7 (0.03)	2.7 (0.02)	.93	2.9 (0.08)	3.0 (0.05)	.11

Abbreviations: ms, milliseconds; NCV, nerve conduction velocity; PAD, peripheral arterial disease.

*Unadjusted data are given as mean (SD) unless otherwise specified.

†Adjusted for age, sex, body mass index, race, cigarette smoking, comorbidities, height, alcohol consumption, recruitment cohort, lower extremity revascularization. Adjusted data are given as mean (SE) unless otherwise specified.

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Table 4

Adjusted Associations Between the ABI and Nerve Function in Persons With Peripheral Arterial Disease*

Nerve Function	ABI, <0.50 (n = 72)	ABI, 0.50 to <0.70 (n = 132)	ABI, 0.70 to <0.90 (n = 117)	*P* Value for Trend
Nondiabetic Participants				
Peroneal NCV	42.2 (41.1–43.3)	43.8 (43.1–44.6)†	44.6 (43.8–45.4)‡	.001
Peroneal nerve amplitude	2.5 (2.0–3.1)	3.2 (2.8–3.6)§	3.5 (3.1–3.9) ‖	.009
Peroneal nerve latency	5.0 (4.8–5.2)	4.8 (4.7–4.9)	4.8 (4.6–4.9)	.11
Sural NCV	3.7 (39.3–43.5)	42.1 (40.7–43.4)	42.8 (41.3–44.3)	.28
Sural nerve amplitude	5.0 (3.5–6.4)	5.6 (4.6–6.7)	6.1 (5.1–7.2)	.22
Sural nerve latency	3.7 (3.3–4.1)	3.5 (3.2–3.7)	3.4 (3.1–3.6)	.17
Ulnar NCV	51.7 (50.6–52.9)	52.1 (51.3–53.0)	52.1 (51.2–53.0)	.66
Ulnar sensory nerve amplitude	17.3 (14.9–19.8)	17.4 (15.7–19.1)	18.1 (16.3–19.9)	.60
Ulnar sensory latency	2.74 (2.68–2.80)	2.71 (2.67–2.76)	2.71 (2.66–2.76)	.50
Diabetic Participants				
Peroneal NCV	40.3 (38.3–42.3)	41.3 (39.9–42.7)	41.2 (39.5–42.9)	.55
Peroneal nerve amplitude	2.4 (1.6–3.2)	2.0 (1.4–2.5)	2.0 (1.4–2.6)	.51
Peroneal nerve latency	5.5 (4.9–6.1)	5.2 (4.8–5.6)	5.0 (4.5–5.5)	.17
Sural NCV	44.5 (38.6–50.4)	41.4 (38.0–44.8)	41.0 (37.0–45.1)	.41
Sural nerve amplitude	4.1 (2.5–5.7)	2.7 (1.6–3.8)	4.0 (2.8–5.2)	.84
Sural nerve latency	3.2 (−1.9–8.4)	3.7 (0.7–6.6)	5.9 (2.4–9.4)	.33
Ulnar NCV	48.7 (46.2–51.2)	47.8 (46.1–49.6)	46.8 (44.9–48.7)	.23
Ulnar sensory nerve amplitude	16.7 (12.4–21.0)	14.4 (11.5–17.4)	10.9 (7.7–14.1)¶	.03
Ulnar sensory latency	2.9 (2.7–3.2)	3.0 (2.8–3.1)	3.2 (3.0–3.3)	.10

Abbreviations: ABI, ankle brachial index; NCV, nerve conduction velocity.

*Data are given as mean (95% confidence interval). Data are adjusted for age, sex, race, height, cigarette smoking, body mass index, number of cardiac or cerebrovascular diseases, history of lower extremity revascularization, disk disease, spinal stenosis, number of alcoholic drinks consumed per day, and cohort source. *P* values for comparisons among participants with peripheral arterial disease include statistical adjustment for leg symptoms.

†*P* = .03 for pairwise comparison with the ABI lower than 0.50 group.

‡*P* = .001 for pairwise comparison with the ABI lower than 0.50 group.

§*P* = .05 for pairwise comparison with the ABI lower than 0.50 group.

‖*P* = .007 for pairwise comparison with the ABI lower than 0.50 group.

¶*P* = .04 for pairwise comparison with the ABI lower than 0.50 group.

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Table 5

Bilateral Lower Extremity Nerve Function in Nondiabetic PAD Participants With Differences in ABI of 0.20 or Higher Between the Right and Left Legs

Nerve Function	No. of Participants*	Leg With Higher ABI, Mean (SD)	Leg With Lower ABI, Mean (SD)	*P* Value
Peroneal NCV, m/s	88	44.6 (4.7)	43.7 (4.6)	.01
Peroneal nerve amplitude, μV	102	3.26 (2.48)	2.82 (2.33)	.04
Peroneal nerve latency, ms	88	4.95 (1.02)	5.06 (0.96)	.26
Sural nerve NCV, m/s	66	42.4 (6.0)	42.0 (6.6)	.44
Sural nerve amplitude, μV	101	4.60 (4.26)	5.55 (7.69)	.18
Sural nerve latency, ms	66	3.36 (0.47)	3.41 (0.51)	.29

Abbreviations: ABI, ankle brachial index; ms, millisecond; NCV, nerve conduction velocity; PAD, peripheral arterial disease.

*Participants without response to stimulation were considered to have a “zero” value for amplitude but were considered to have missing data for NCV and latency analyses.