Exertional Leg Symptoms Other Than Intermittent Claudication Are Common in Peripheral Arterial Disease

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Background: Epidemiological data show that most community-dwelling men and women with lower-extremity peripheral arterial disease (PAD) do not have typical symptoms of intermittent claudication. We compared the prevalence of intermittent claudication, leg symptoms other than intermittent claudication, and absence of exertional leg symptoms between patients with PAD identified from a blood flow laboratory (group 1), patients with PAD in a general medicine practice (group 2), and control patients without PAD (group 3).

Methods: Numbers of participants in groups 1, 2, and 3 were 137, 26, and 105, respectively. Patients with previously diagnosed PAD were excluded from groups 2 and 3. All participants underwent ankle-brachial index measurement and were administered the San Diego claudication questionnaire to assess leg symptoms.

Results: Within groups 1, 2, and 3, prevalences of intermittent claudication were 28.5% (n = 39), 3.8% (n = 1), and 3.8% (n = 4), respectively. Prevalences of exertional leg symptoms other than intermittent claudication were 56.2% (n = 77), 42.3% (n = 11), and 19.0% (n = 20), respectively. Absence of exertional leg symptoms was reported by 15.3% (n = 21), 53.8% (n = 14), and 77.1% (n = 81), respectively. Among patients with PAD, older age, male sex, diabetes mellitus, and group 2 vs group 1 status were associated independently with absence of exertional leg symptoms in multivariable regression analysis. Lower ankle-brachial index levels and group 1 vs group 2 status were associated with intermittent claudication.

Conclusions: Clinical manifestations of PAD are diverse, particularly among patients identified by ankle-brachial index screening. Exertional leg symptoms other than intermittent claudication are common in PAD. Patients with PAD who are older, male, diabetic, or identified with ankle-brachial index screening in a primary care setting are more likely to have asymptomatic PAD.

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Lower-extremity peripheral arterial disease (PAD) can be accurately, noninvasively diagnosed with the ankle-brachial index (ABI), a ratio of Doppler-recorded systolic pressures in the lower and upper extremities. Intermittent claudication has been considered the most characteristic manifestation of PAD and is defined as ischemic calf pain precipitated by walking and relieved within 10 minutes of rest. However, in community-based epidemiological studies, most people with a low ABI consistent with PAD do not have classic intermittent claudication. It is unclear whether these men and women with low ABI unaccompanied by claudication are asymptomatic or have leg symptoms other than claudication.

Based on noninvasive testing with the ABI, a previous study showed that nearly 25% of men and women aged 55 years and older in general medicine practices have PAD. A clearer understanding of the spectrum of leg symptoms associated with PAD may aid clinicians in recognizing and diagnosing PAD. Among patients with coronary artery disease, atypical symptoms and asymptomatic disease are frequent. In a similar manner, atypical symptoms may also occur in PAD, but this issue has not been well studied.

We studied the prevalence of classic intermittent claudication, exertional leg symptoms other than intermittent claudication, and absence of exertional leg symptoms among patients with PAD identified from a blood flow laboratory, patients with PAD identified with ABI...
SUBJECTS AND METHODS

SUBJECT IDENTIFICATION

The study protocol was approved by the institutional review board. This study was part of a prospective study of lower-extremity functioning and PAD at Northwestern University Medical Center, Chicago, Ill. Consecutive patients aged 55 years and older diagnosed as having PAD at the study institution’s blood flow laboratory between January 1, 1996, and approximately November 1, 1996, were identified by means of computerized lists and enrolled between January 1, 1996, and July 31, 1997. Men and women aged 55 years and older with upcoming appointments in general internal medicine were identified and randomly selected by means of a computer program between January 1, 1996, and March 31, 1998. Identified patients were mailed an informational letter describing the study, telephoned within 2 to 4 weeks after the mailing, and invited to return to the medical center for a study visit. Beginning in August 1997, patients with ABI of 0.90 or greater identified from general medicine were randomly selected for complete data collection. All patients with ABI less than 0.90 in general medicine who met inclusion criteria were enrolled. The prevalence of ABI less than 0.90 among men and women aged 55 years and older in general medicine without a history of PAD was 12%. To increase the prevalence of ABI less than 0.90, patients aged 60 years and older were enrolled from general medicine during the last 5 months of data collection.

EXCLUSION CRITERIA

We excluded patients with a Mini-Mental Status Examination score less than 18 of 30.19 Nursing home residents, wheelchair-bound patients, and patients with foot or leg amputations were excluded, because these individuals have uniquely impaired functioning. Patients with lower-extremity ulcers were excluded, because blood pressure cuffs cannot be placed over ulcers for ABI measurement. Non–English-speaking patients were excluded, because study investigators were not fluent in non-English languages, and patients with a life expectancy less than 6 months were excluded, because of their limited likelihood of follow-up. Patients with ABI of 1.50 or greater were excluded, because their arteries are often incompressible, preventing accurate assessment of lower-extremity arterial perfusion. Among patients identified from general medicine, those with a history of PAD were excluded. History of PAD was defined as (1) previous lower-extremity revascularization, (2) patient report of a physician-rendered diagnosis of intermittent claudication or poor leg circulation, or (3) medical record documentation of PAD.

ABI MEASUREMENT

The ABI was measured on all patients by previously described methods.10 Patients were categorized according to their ABI level and recruitment site. Group 1 included patients identified from the blood flow laboratory with ABI less than 0.90. Group 2 consisted of patients identified from general medicine with ABI less than 0.90. Group 3 consisted of patients identified from general medicine with ABI of 0.90 or greater and less than 1.50.

DEFINITIONS OF COMORBID DISEASE

Medical record review and a primary care physician questionnaire were used to identify comorbidities, according to definitions and methods in the Women’s Health and Aging Study.20 Diabetes mellitus required at least 1 of the following: (1) use of insulin or an oral hypoglycemic agent, (2) medical record–documented hemoglobin A1c level greater than 10%, or (3) diabetes mellitus documented in the primary care physician questionnaire. Hypercholesterolemia was defined by use of lipid-lowering drugs or medical record documentation of a total cholesterol level greater than 6.45 mmol/L (250 mg/dL). Cigarette smoking was based on patient report. Regular exercise was defined as aerobic activity for the purpose of exercise performed at least 3 times weekly for at least 30 minutes each time.

LEG SYMPTOM DEFINITIONS

Patients’ leg symptoms were classified into categories by means of the San Diego claudication questionnaire, based on previous work by Criqui et al.21 (Table 1). The claudication

screening in a general internal medicine practice, and patients without PAD at an academic medical center. Among patients with PAD, we identified clinical characteristics associated with (1) absence of exertional leg symptoms and (2) presence of intermittent claudication. On the basis of studies of patients with coronary artery disease, we hypothesized that older patients and patients with diabetes mellitus would be more likely to be asymptomatic.17,18 We further hypothesized that lower ABIs and current cigarette smoking would be associated with intermittent claudication.

RESULTS

Of 485 consecutive patients aged 55 years and older with PAD identified in the blood flow laboratory during 1996, 74 met 1 or more exclusion criteria. In addition, 23 were deceased, 61 could not be reached, 82 refused participation, 37 were limited in transportation, 42 could not be scheduled during the enrollment period, and 29 did not keep study appointments, leaving a total of 137 patients with PAD in group 1. Of 411 randomly selected men and women aged 55 years and older with pending appointments in general internal medicine, 56 met exclusion criteria. Of the 56 excluded, 22 had a previous history of PAD. In addition, 109 refused participation, 12 had incorrect or disconnected phone numbers, 1 was deceased, and 33 did not keep study appointments, leaving 200 subjects. Of these, 69 had a normal ABI and were not randomly selected for further study, and 26 (13%) had an ABI less than 0.90 and were categorized into group 2. The remaining 105 patients with ABI of 0.90 or greater and less than 1.50 were categorized into group 3.
questionnaire was administered before ABI measurement. Study investigators were blinded to the presence vs absence of PAD when they administered the questionnaire to general medicine patients. Questionnaire administrators were not blinded to the presence vs absence of PAD among patients recruited from the blood flow laboratory.

Leg symptom categories and their definitions were as follows: (1) no exertional leg pain, defined as the absence of exertional leg pain, numbness, or discomfort; (2) atypical exertional leg pain, defined as (a) exertional calf symptoms that do not begin at rest but are otherwise not consistent with Rose intermittent claudication or (b) exertional leg symptoms that do not begin at rest and do not include the calves; (3) pain at rest: exertional leg symptoms that also begin at rest; and (4) Rose intermittent claudication: exertional calf symptoms that do not begin at rest, worsen when walking uphill or hurrying, and resolve within 10 minutes of rest. This definition of Rose claudication questionnaire is 91% sensitive and 67.5% specific for clinician-diagnosed claudication.

STATISTICAL ANALYSES

We used χ² tests of association to compare the prevalence of clinical characteristics and leg symptoms between groups 1, 2, and 3. Because no patients had different types of leg symptoms in each leg, 1 P value was calculated to compare leg symptoms between the 3 groups. Logistic regression was used to identify independent predictors of absence of exertional leg symptoms and intermittent claudication among patients with PAD, controlling for sex, age, race, exercise, current smoking, hypercholesterolemia, diabetes mellitus, past lower-extremity revascularization, pentoxifylline use, ABI, and group 2 vs group 1 status. Because pentoxifylline is the only medication consistently associated with a significant effect on claudication symptoms, we adjusted for pentoxifylline but not other medications in regression analyses. Additional logistic regression analyses were performed to determine whether exercise frequency or exercise duration was independently associated with leg symptoms.

CHARACTERISTICS OF STUDY PATIENTS

Table 2 compares clinical characteristics and the prevalence of leg symptoms between groups 1, 2, and 3. Compared with group 1, group 2 patients were less likely to have classic symptoms of intermittent claudication and more likely to have absence of exertional leg symptoms.

REGRESSION ANALYSES

Table 3 shows results of multivariable logistic regression analyses relating clinical characteristics to absence of exertional leg symptoms and presence of intermittent claudication, respectively, among PAD patients. Older age, male sex, diabetes mellitus, and group 2 vs group 1 status were associated independently with absence of exertional leg symptoms. Lower ABI and group 1 vs group 2 status were associated independently with intermittent claudication. In additional regression analyses, increasing exercise duration was associated significantly with intermittent claudication symptoms (odds ratio, 1.33; P = .03). There were no other independent relationships between exercise frequency or duration and intermittent claudication or absence of exertional leg symptoms.

COMMENT

Intermittent claudication is considered the most classic manifestation of PAD and is described as the “earliest manifestation” or “most common symptom” in PAD. However, among white women participating in the Study of Osteoporotic Fractures, only 18% of...
women found to have PAD by ABI screening had intermittent claudication. Similarly, in the Cardiovascular Health Study, 12% of men and women aged 65 years and older had an abnormally low ABI, while just 2% had in-

Table 2. Characteristics and Leg Symptoms Among Patients With Peripheral Arterial Disease and Controls*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (n = 137)</th>
<th>Group 2 (n = 26)</th>
<th>Group 3 (n = 105)</th>
<th>Trend P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>71.9 ± 9.8</td>
<td>69.0 ± 6.5</td>
<td>68.0 ± 7.2</td>
<td>.002</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>80 (58.4)</td>
<td>8 (30.8)</td>
<td>47 (44.8)</td>
<td>.01</td>
</tr>
<tr>
<td>Ankle-brachial index, mean ± SD</td>
<td>0.55 ± 0.18</td>
<td>0.71 ± 0.26</td>
<td>1.06 ± 0.09</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>African American race, No. (%)</td>
<td>19 (13.9)</td>
<td>12 (46.2)</td>
<td>23 (21.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Regular exercise, No. (%)</td>
<td>35 (25.5)</td>
<td>7 (26.9)</td>
<td>34 (32.4)</td>
<td>.50</td>
</tr>
<tr>
<td>Current smokers, No. (%)</td>
<td>29 (21.2)</td>
<td>5 (19.2)</td>
<td>7 (6.7)</td>
<td>.007</td>
</tr>
<tr>
<td>Diabetes mellitus, No. (%)</td>
<td>38 (27.7)</td>
<td>6 (23.1)</td>
<td>17 (16.2)</td>
<td>.11</td>
</tr>
<tr>
<td>Hypercholesterolemia, No. (%)</td>
<td>82 (59.9)</td>
<td>13 (50.0)</td>
<td>44 (41.9)</td>
<td>.02</td>
</tr>
<tr>
<td>Leg symptoms, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No exertional leg symptoms</td>
<td>21 (15.3)</td>
<td>14 (53.8)</td>
<td>81 (77.1)</td>
<td>NC</td>
</tr>
<tr>
<td>Atypical exertional leg symptoms</td>
<td>35 (25.5)</td>
<td>2 (7.7)</td>
<td>5 (4.8)</td>
<td>.001</td>
</tr>
<tr>
<td>Pain at rest</td>
<td>42 (30.7)</td>
<td>9 (34.6)</td>
<td>15 (14.3)</td>
<td>NC</td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>39 (28.5)</td>
<td>1 (3.8)</td>
<td>4 (3.8)</td>
<td>NC</td>
</tr>
</tbody>
</table>

*Group 1, patients with peripheral arterial disease (ankle-brachial index < 0.90) identified from the blood flow laboratory; group 2, patients with peripheral arterial disease identified from a general internal medicine practice via ankle-brachial index screening; and group 3, patients without peripheral arterial disease (ankle-brachial index, 0.90-1.50) identified from general internal medicine. Differences in leg symptoms between group 1, group 2, and group 3 are significant at P < .05. All patients with bilateral exertional leg symptoms had the same type of symptoms in each leg. Therefore, the P value represents differences in all leg categories between groups 1, 2, and 3, and separate P values were not calculated (NC) for each category of leg symptoms. Percentages do not add to 100% because of rounding.

unclear. Among participants with PAD in the Cardiovascular Health Study and the Study of Osteoporotic Fractures, 40% and 45%, respectively, had an ABI of 0.80 or greater and less than 0.90, indicative of mild disease. In contrast, 14% of patients with PAD in the present study had an ABI of 0.80 or greater and less than 0.90. Thus, most patients with PAD described herein had more severe disease than the previously described men and women with PAD in epidemiological studies.

The most striking implication of our data is that the clinical manifestations of PAD are diverse among patients with ABI less than 0.90 at an academic medical center. Identifying the full spectrum of PAD requires attention to symptoms other than classic intermittent claudication and possibly screening for PAD even among asymptomatic patients. In the present study, 29% of patients with PAD identified from the blood flow laboratory had classic intermittent claudication, compared with 4% of patients with PAD identified with ABI screening in a general internal medicine practice and 4% of normal controls. Thus, the sensitivity of intermittent claudication for PAD appears higher in a blood flow laboratory setting than among patients with PAD identified with ABI screening from a general medicine practice. This discrepancy is in part caused by selection bias, since all patients with PAD recruited from the blood flow laboratory were referred by a physician who suspected PAD, whereas patients identified from general internal medicine had previously unrecognized disease. The PAD may have been unrecognized among general medicine patients in part because 96% did not have typical intermittent claudication symptoms.

The high prevalence of pain at rest among patients with PAD in a general medicine practice was unexpected and should be distinguished from PAD-related rest pain, a symptom of severe ischemic disease that typically increases when the affected leg is elevated. In our study, pain at rest was defined as any exertional leg pain that also occurs at rest. Since none of the patients with
PAD from general medicine had previously diagnosed disease, it is highly unlikely that these patients were experiencing severe ischemia. Perhaps patients with PAD recruited from general medicine were experiencing mild arterial ischemia at rest. Alternatively, they may have confused other types of pain occurring at rest with their exertional leg symptoms.

While comorbid diseases may contribute to the high prevalence of exertional leg symptoms other than intermittent claudication in PAD, at least 2 factors make this unlikely. Aside from diabetic neuropathy, we know of no biologically plausible explanation for a higher prevalence of comorbidities causing exertional leg symptoms, such as spinal stenosis or lower-extremity arthritis, among patients with PAD as compared with patients without PAD. Although diabetic neuropathy might increase the prevalence of atypical exertional leg symptoms or pain at rest, our logistic regression analysis showed that diabetes mellitus was associated independently with asymptomatic PAD. Therefore, our comparisons of leg symptoms between PAD and control patients should represent valid differences in leg symptoms caused by the presence or absence of PAD.

Our data suggest that among patients with PAD, older age, diabetes mellitus, male sex, and ABI screening in a general medicine practice are associated with absence of exertional leg symptoms. The association between asymptomatic PAD and older age may in part be caused by lower activity levels among the elderly, since greater physical activity levels may be necessary to induce exertional leg symptoms. Similarly, increasing exercise duration may be more likely to precipitate lower-extremity arterial ischemia, accounting for the positive relationship observed between exercise duration and intermittent claudication. Our data suggest that screening for PAD with the ABI may be especially useful among older, diabetic, male patients in a general medicine setting. Physical examination is neither sensitive nor specific for diagnosing PAD in community-based or hospital settings.11,26

We are aware of only 1 other report describing the spectrum of leg symptoms among patients with PAD in a patient care setting.21 Criqui et al described leg symptoms in a blood flow laboratory population including 88% men and 4% African Americans. Criqui et al reported a 26% prevalence of intermittent claudication and a 25% prevalence of pain at rest. Although their results are generally consistent with ours, the 31% prevalence of asymptomatic PAD reported by Criqui et al is twice that reported herein for patients from a blood flow laboratory. Our data add to the work of Criqui et al by assessing the prevalence of leg symptoms among patients with PAD in a general medical setting and control patients without PAD.

Our study had a few limitations. Our data reflect patients at 1 medical center, and results may not be generalizable to patients with PAD at other institutions. Exclusion of non–English-speaking patients may limit the generalizability of our findings to patients who do not speak English. However, the consistency of our findings for patients with PAD from a blood flow laboratory with those reported by Criqui et al suggests that our data are similar to those of other academic medical centers.21 Second, many potentially eligible subjects could not be reached, refused participation, or had transportation difficulties, limiting study enrollment. Severity of PAD was comparable between potentially eligible patients with PAD and participating patients with PAD from the blood flow laboratory. Potentially eligible patients with PAD who refused participation were slightly older than participants with PAD from the blood flow laboratory. Because increasing age was associated with a lower prevalence of exertional leg symptoms, it is conceivable that our results underestimate the prevalence of asymptomatic PAD among patients at a blood flow laboratory. Finally, the absolute number of patients with PAD identified with ABI screening in general medicine was small. Further study is necessary to confirm our findings for patients with PAD identified with ABI screening from primary care physicians’ practices.

The 13% prevalence of previously undiagnosed PAD among men and women in our general medicine practice suggests that PAD may regularly go unrecognized in primary care settings, perhaps because the high prevalence of asymptomatic disease and exertional leg symptoms other than intermittent claudication are underappreciated by clinicians. Recognizing PAD, even when asymptomatic, is important because PAD has significant implications for cardiovascular morbidity and mortality.27 Our data highlight the need for a better understanding of the spectrum of clinical pictures presented by a broad range of patients with PAD.

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Reprints not available from the authors.

REFERENCES


