Review Article

Management of Peripheral Arterial Disease of the Lower Extremities in Elderly Patients

Wilbert S. Aronow

Divisions of Cardiology and Geriatrics, Department of Medicine, New York Medical College, Valhalla.

The prevalence of peripheral arterial disease (PAD) increases with age. PAD in elderly persons may be asymptomatic, may be associated with intermittent claudication, or may be associated with critical limb ischemia. Other atherosclerotic vascular disorders, especially coronary artery disease (CAD), may coexist with PAD. Elderly persons with PAD are at increased risk for all-cause mortality, cardiovascular mortality, and mortality from CAD. Modifiable risk factors should be treated in persons with PAD such as cessation of cigarette smoking and control of hypertension, dyslipidemia, and diabetes. Statins have been shown to reduce the incidence of intermittent claudication and to improve treadmill exercise duration until the onset of intermittent claudication in persons with PAD and hypercholesterolemia. Antiplatelet drugs such as aspirin or clopidogrel, especially clopidogrel, should be administered to all persons with PAD. Persons with PAD should be treated with angiotensin-converting enzyme inhibitors and also with beta blockers if CAD is present. Cilostazol should be given to persons with intermittent claudication to improve exercise capacity unless heart failure is present. Exercise rehabilitation programs improve exercise time until claudication. Indications for lower extremity angioplasty, preferably with stenting, or bypass surgery are 1) incapacitating claudication in persons interfering with work or lifestyle; 2) limb salvage in persons with limb-threatening ischemia as manifested by rest pain, nonhealing ulcers, and/or infection or gangrene; and 3) vasculogenic impotence. However, amputation should be performed if tissue loss has progressed beyond the point of salvage, if surgery is too risky, if life expectancy is very low, or if functional limitations obviate the benefit of limb salvage.

Peripheral arterial disease (PAD) is chronic arterial occlusive disease of the lower extremities caused by atherosclerosis. PAD may cause intermittent claudication, which is pain or weakness with walking that is relieved with rest. The muscle pain or weakness induced by exercise occurs distal to the arterial obstruction. Since the superficial femoral and popliteal arteries are most commonly affected by atherosclerosis, the pain of intermittent claudication is most commonly localized to the calf. Atherosclerotic obstruction of the distal aorta and its bifurcation into the two iliac arteries may cause pain in the buttocks or thighs as well as the legs. Only one half of elderly patients with documented PAD are symptomatic. Patients with PAD may not walk far or fast enough to induce muscle ischemic symptoms because of comorbidities such as arthritis or pulmonary disease, may have atypical symptoms unrecognized as intermittent claudication (1), may fail to mention their symptoms to their physician, or may have sufficient collateral arterial channels to tolerate their arterial obstruction. If the arterial flow to the lower extremities cannot meet the needs of resting tissue metabolism, critical lower extremity ischemia occurs. Critical ischemia causes rest pain in the toes or foot with progression to ulceration or gangrene. Chronic arterial insufficiency ulcers commonly develop at the ankle, heel, or leg. Mummified, dry, black toes or devitalized soft tissue covered by a crust is gangrene resulting from ischemic infarction. Suppuration often develops with time, and dry gangrene changes to wet gangrene.

Noninvasive Diagnosis

Persons with PAD of the lower extremities have diminished or absent arterial pulses. Noninvasive tests used to assess lower extremity arterial blood flow include measurement of ankle and brachial artery systolic blood pressures, characterization of velocity wave form, and duplex ultrasonography. Measurement of ankle and brachial artery systolic blood pressures using a Doppler stethoscope and blood pressure cuffs allows calculation of the ankle/brachial index (ABI), which is normally 0.9 to 1.2. An ABI of less than 0.90 is 95% sensitive and 99% specific for the diagnosis of PAD (2). The lower the ABI, the more severe the restriction of arterial blood flow, and the more serious the ischemia. With ABIs between 0.25 to 0.4, rest pain and tissue loss are often found. Patients with calcified arteries from diabetes mellitus or renal failure occasionally have relatively noncompressible arteries leading to falsely elevated ABI values in the normal range.

In addition to measuring arterial pressure in nonpalpable arteries, Doppler ultrasound methods allow characterization of the flow versus time velocity waveform. Finding biphasic flow at the groin or monophasic flow more distally is evidence of arterial obstruction even when ABI measurements are falsely increased to normal levels because of calcification.
Table 1. Prevalence of Peripheral Arterial Disease in Older Persons

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>158 persons aged 38–59 years (4)</td>
<td>5.6%</td>
</tr>
<tr>
<td>161 persons aged 60–69 years (4)</td>
<td>15.9%</td>
</tr>
<tr>
<td>294 persons aged 70–82 years (4)</td>
<td>33.8%</td>
</tr>
<tr>
<td>2214 men aged ≥65 years (5)</td>
<td>13.9%</td>
</tr>
<tr>
<td>2870 women aged ≥65 years (5)</td>
<td>11.4%</td>
</tr>
<tr>
<td>467 men, mean age 80 years (6)</td>
<td>20%*</td>
</tr>
<tr>
<td>1444 women, mean age 81 years (6)</td>
<td>13%*</td>
</tr>
<tr>
<td>2589 men aged ≥55 years (7)</td>
<td>16.9%</td>
</tr>
<tr>
<td>3861 women aged ≥55 years (7)</td>
<td>20.5%</td>
</tr>
<tr>
<td>1160 men, mean age 80 years (8)</td>
<td>32%*</td>
</tr>
<tr>
<td>2464 women, mean age 81 years (8)</td>
<td>26%*</td>
</tr>
</tbody>
</table>

Notes: *Symptomatic peripheral arterial disease. Numbers in parentheses are reference numbers.

Duplex ultrasonography combines Doppler frequency measurements with two-dimensional images of blood vessels. The severity of flow restriction induced by an arterial stenosis can be accurately assessed by this most comprehensive noninvasive method (3).

**Prevalence**

The prevalence of PAD increases with age. Criqui and colleagues (4) reported that the prevalence of PAD was 5.6% in persons aged 38 to 59 years old, 15.9% in persons aged 60 to 69 years old, and 33.8% in persons aged 70 to 82 years old (Table 1). In the Cardiovascular Health Study, PAD was present in 13.9% of 2214 men aged ≥65 years and in 11.4% of 2870 women aged ≥65 years without cardiovascular disease (5) (Table 1). Symptomatic PAD was present in 20% of 467 men, mean age 80 years, and in 13% of 1444 women, mean age 81 years, living in the community and being seen in a geriatrics clinic (6) (Table 1). In the Rotterdam Study, PAD was present in 16.9% of 2589 men aged ≥55 years and in 20.5% of 3861 women aged ≥55 years (7) (Table 1). The prevalence of symptomatic PAD was 32% in 1160 men, mean age 80 years, and 26% in 2464 women, mean age 81 years, living in a nursing home (8) (Table 1).

**Risk Factors**

Modifiable risk factors that predispose to PAD include cigarette smoking (6,9–15), diabetes mellitus (6,9–16), hypertension (6,9,10,14,15,17,18), dyslipidemia (6,9,10,12–16,19–21), increased plasma homocysteine levels (22–25), and hypothyroidism (26). Table 2 shows that significant independent risk factors for PAD in 467 men, mean age 80 years, and in 1444 women, mean age 81 years, living in the community and seen in an academic geriatrics practice were age (odds ratio = 1.05 for each 1-year increase in age in men and 1.03 for each 1-year increase in age in women); current cigarette smoking (odds ratio = 2.6 for men and 4.6 for women); hypertension (odds ratio = 2.2 for men and 2.8 for women); diabetes mellitus (odds ratio = 6.1 for men and 3.6 for women); serum high-density lipoprotein cholesterol (odds ratio = 0.95 for each 1 mg/dl increase in men and 0.97 for each 1 mg/dl increase in women); and serum low-density lipoprotein cholesterol (odds ratio = 1.02 for each 1 mg/dl increase in men and women) (6).

In 520 men and women (147 with PAD), mean age 81 years, plasma homocysteine was a significant independent risk factor for PAD with an odds ratio of 1.13 for each 1 μmol/l increase (25). In 249 men and women, mean age 79 years, the prevalence of PAD was significantly higher in persons with subclinical hypothyroidism (14 of 18 persons or 78%) than in persons with euthyroidism (40 of 231 persons or 17%) (26).

**Coexistence of Other Atherosclerotic Disorders**

PAD coexists with other atherosclerotic disorders (Table 3) (27–31). In a study of 1886 men and women, mean age 81 years, 270 of 468 persons (58%) with PAD had coexistent coronary artery disease (CAD) and 159 of 468 persons (34%) with PAD had prior ischemic stroke (Table 3) (27). In a study of 1802 men and women, mean age 80 years, living in the community and seen in an academic geriatrics practice, 161 of 236 persons (68%) with PAD had coexistent CAD and 100 of 236 persons (42%) with PAD had coexistent prior ischemic stroke (Table 3) (28).

In 924 men, mean age 80 years, the prevalence of PAD was 1.5 times significantly higher in 336 men with mitral annular calcium than in 588 men without mitral annular calcium (43% versus 28%) (Table 3) (29). In 1881 women, mean age 81 years, the prevalence of PAD was 1.6 times significantly higher in 985 women with mitral annular calcium than in 896 women without mitral annular calcium (31% versus 19%) (Table 3) (29).

In 989 men, mean age 80 years, the prevalence of PAD was 1.6 times significantly higher in 141 men with valvular aortic stenosis than in 848 men without valvular aortic stenosis (48% versus 30%) (Table 3) (30). In 1998 women, mean age 81 years, the prevalence of PAD was 1.7 times significantly higher in 321 women with valvular aortic stenosis than in 1677 women without valvular aortic stenosis (39% versus 23%) (Table 3) (30).

In 279 men and women, mean age 71 years, with documented PAD, and in 218 men and women, mean age 70 years, without PAD with normal ABIs undergoing coronary angiography for suspected CAD, the incidence of obstructive CAD was significantly higher in persons with PAD (98%) than in persons without PAD (81%) (Table 3) (31). The incidence of 3-vessel or 4-vessel CAD was significantly...
higher in persons with PAD (63%) than in persons without PAD (11%) (Table 3) (31).

CARDIOVASCULAR MORTALITY AND MORBIDITY

Persons with PAD are at increased risk for all-cause mortality, cardiovascular mortality, and cardiovascular events (32–39). At 10-year follow-up of 565 men and women, mean age 66 years, PAD significantly increased the risk of all-cause mortality (relative risk = 3.1), of mortality from cardiovascular disease (relative risk = 5.9), and of mortality from CAD (relative risk = 6.6) (32). At 4-year follow-up of 1492 women, mean age 71 years, an ABI of 0.9 or less was associated with a relative risk of 3.1 for all-cause mortality after adjustment for age, smoking, and other risk factors (35).

In a prospective study of 291 men and women, mean age 82 years, with PAD, CAD was present in 160 persons (55%) (34). Silent myocardial ischemia detected by 24-hour ambulatory electrocardiography was present in 60 of 160 persons (38%) with PAD and CAD and in 26 of 131 persons (20%) with PAD and no clinically evident CAD (34). At 43-month follow-up, new coronary events developed in 54 of 60 persons (90%) with PAD, CAD, and silent myocardial ischemia, and in 59 of 100 persons (59%) with PAD, CAD, and no silent myocardial ischemia (34). New coronary events also developed in 18 of 26 persons (69%) with PAD, no CAD, and silent myocardial ischemia, and in 34 of 105 persons (32%) with PAD, no CAD, and no silent myocardial ischemia (34).

RISK FACTOR MODIFICATION

Continuing smoking increases the risk of amputation in patients with intermittent claudication (40). Patency in lower extremity bypass grafts is also worse in smokers than in nonsmokers (41). Smoking cessation slows the progression of PAD to critical leg ischemia and decreases the risk of myocardial infarction and death from vascular causes (42). Smoking cessation programs should be strongly encouraged in persons with PAD.

There are no good data showing that drug treatment of hypertension or diabetes mellitus will favorably affect the progression of PAD. However, hypertension should be adequately controlled to prevent cardiovascular mortality and morbidity in persons with PAD (17,18,43). Diabetes mellitus should also be controlled with the hemoglobin A1c level reduced to less than 7% to reduce the incidence of myocardial infarction (44).

Treatment of dyslipidemia with statins has been demonstrated to reduce the incidence of mortality, cardiovascular events, and stroke in persons with PAD and without CAD (20,21,45–52). At 5-year follow-up of 4444 men and women with CAD and hypercholesterolemia in the Scandinavian Simvastatin Survival Study, compared with placebo, simvastatin significantly reduced the incidence of intermittent claudication by 38% (45).

In a study of 264 men and 396 women, mean age 80 years, with symptomatic PAD and a serum low-density lipoprotein cholesterol of 125 mg/dl or higher, 318 of 660 persons (48%) were treated with a statin and 342 of 660 persons (52%) with no lipid-lowering drug (50). At the 39-month follow-up, treatment with statins caused a significant independent reduction in the incidence of new coronary events of 58%, of 52% in persons with prior myocardial infarction, and of 59% in persons with no prior myocardial infarction (50).

In a prospective study of 69 patients, mean age 75 years, with intermittent claudication, a mean ABI of 0.63, and a serum low-density lipoprotein cholesterol of 125 mg/dl or higher, 34 persons were randomized to simvastatin 40 mg daily and 35 persons to placebo after baseline treadmill exercise tests until the onset of intermittent claudication (53). Three of 34 persons (9%) treated with simvastatin and 6 of 35 persons (17%) treated with placebo died before the 1-year study was completed (53). Compared with placebo, simvastatin significantly increased the treadmill exercise time until the onset of intermittent claudication by 24% at 6 months and by 42% at 1 year after treatment (53).

On the basis of the available data, persons with PAD and hypercholesterolemia should be treated with statins to reduce cardiovascular mortality and morbidity and progression of PAD and to improve exercise time until claudication in persons with intermittent claudication. Since lipid-lowering therapy is underutilized in elderly persons with PAD (54,55), intensive educational programs are needed to educate physicians to use lipid-lowering therapy in elderly persons with cardiovascular disease and dyslipidemia (55–57).

<p>| Table 3. Coexistence of Peripheral Arterial Disease With Other Atherosclerotic Disorders in Older Persons |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1886 persons, mean age 81 years (27)</td>
<td>If PAD was present, 58% had coexistent CAD and 34% had prior ischemic stroke</td>
</tr>
<tr>
<td>1802 persons, mean age 80 years (28)</td>
<td>If PAD was present, 68% had coexistent CAD and 42% had prior ischemic stroke</td>
</tr>
<tr>
<td>924 men, mean age 80 years (29)</td>
<td>PAD was 1.5 times higher in men with mitral annular calcium than in men without mitral annular calcium</td>
</tr>
<tr>
<td>1881 women, mean age 81 years (29)</td>
<td>PAD 1.6 times higher in women with mitral annular calcium than in women without mitral annular calcium</td>
</tr>
<tr>
<td>989 men, mean age 80 years (30)</td>
<td>PAD was 1.6 times higher in men with aortic stenosis than in men without aortic stenosis</td>
</tr>
<tr>
<td>1998 women, mean age 81 years (30)</td>
<td>PAD was 1.7 times higher in women with aortic stenosis than in women without aortic stenosis</td>
</tr>
<tr>
<td>279 persons with PAD, mean age 71 years, undergoing coronary angiography for suspected CAD</td>
<td>Obstructive CAD was present in 98% of persons and 3- or 4-vessel CAD was present in 63% of persons</td>
</tr>
<tr>
<td>218 persons without PAD, mean age 70 years, undergoing coronary angiography for suspected CAD</td>
<td>Obstructive CAD was present in 82% of persons and 3- or 4-vessel CAD was present in 11% of persons</td>
</tr>
</tbody>
</table>

Notes: PAD = peripheral arterial disease; CAD = coronary artery disease. Numbers in parentheses are reference numbers.

ANTIPLATELET DRUGS

If one combines the 42 randomized studies of 9706 patients with intermittent claudication, peripheral arterial grafting, or peripheral angioplasty, the incidence of vascular
Table 4: Indications for Lower Extremity Angioplasty or Bypass Surgery

1. Incapacitating claudication in persons interfering with work or lifestyle
2. Limb salvage in persons with limb-threatening ischemia as manifested by rest pain, nonhealing ulcers, and/or infection or gangrene
3. Vasculogenic impotence

Note: Source: Adapted with permission from Circulation. 1996;94:3026–3049.

death, nonfatal myocardial infarction, and nonfatal stroke at follow-up was significantly reduced 23% by antiplatelet drugs, with similar benefits among patients with intermittent claudication, those having peripheral arterial grafting, and those having peripheral angioplasty (58). These data favor the use of aspirin 160 mg to 325 mg daily in men and women with PAD (58).

Clopidogrel is a thienopyridine derivative that inhibits platelet aggregation by inhibiting the binding of adenosine 5’-diphosphate to its platelet receptor (59). In the Clopidogrel versus Aspirin in Patients at Risk for Ischaemic Events (CAPRIE) trial, 5795 patients with PAD were randomized to clopidogrel 75 mg daily and 5797 patients with PAD were randomized to aspirin 325 mg daily (60). At the 1.9-year follow-up, the annual incidence of vascular death, nonfatal myocardial infarction, and nonfatal stroke was 3.7% in patients randomized to clopidogrel versus 4.9% in patients randomized to aspirin, a 24% significant reduction with the use of clopidogrel (60).

On the basis of these data, it is reasonable to conclude that clopidogrel is superior to aspirin in the treatment of patients with PAD. On the basis of these data, the author also recommends the use of clopidogrel 75 mg daily in the treatment of patients with PAD. However, clopidogrel is much more expensive than aspirin.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

The American College of Cardiology/American Heart Association guidelines recommend treating all persons with atherosclerotic vascular disease with angiotensin-converting enzyme inhibitors unless there are contraindications to the use of these drugs to reduce cardiovascular mortality and morbidity (61).

BETA BLOCKERS

Persons with PAD are at increased risk for developing new coronary events (32–39). Many physicians have been reluctant to use beta blockers in persons with PAD because of concerns that beta blockers will aggravate intermittent claudication. However, a meta-analysis of 11 randomized controlled studies showed that beta blockers do not adversely affect walking capacity or the symptoms of intermittent claudication in persons with mild-to-moderate PAD (62).

An observational study was performed in 575 men and women, mean age 80 years, with symptomatic PAD and prior myocardial infarction (63). Of the 575 patients, 85 (15%) had contraindications to the use of beta blockers. Of the 490 patients without contraindications to the use of beta blockers, 257 (52%) were treated with beta blockers. Adverse effects causing cessation of beta blockers occurred in 31 of the 257 patients (12%). At the 32-month follow-up, use of beta blockers caused a 53% significant independent reduction in the incidence of new coronary events in elderly patients with PAD and prior myocardial infarction (63).

DRUGS TO INCREASE WALKING DISTANCE

Chelation therapy has been demonstrated to be ineffective in the treatment of PAD (64). Numerous drugs have been shown to be ineffective in improving walking distance in patients with intermittent claudication. Most recently, beraprost sodium, an orally active prostaglandin I₂ analogue, was demonstrated to be no more effective than placebo in patients with intermittent claudication (65).

Two drugs, pentoxifylline and cilostazol, have been approved by the United States Food and Drug Administration for symptomatic treatment of intermittent claudication. However, many studies have found no consistent improvement with pentoxifylline in patients with intermittent claudication in comparison with placebo (66,67).

Cilostazol inhibits phosphodiesterase type 3, increasing intracellular concentration of cyclic adenosine monophosphate. Cilostazol suppresses platelet aggregation and also acts as a direct arterial vasodilator. Cilostazol has been demonstrated in numerous trials to improve exercise capacity in patients with intermittent claudication (68–70), and in a dose of 100 mg twice daily, was shown to be superior to both placebo and pentoxifylline (70). However, cilostazol should not be administered to patients with PAD who also have heart failure.

EXERCISE REHABILITATION

Exercise rehabilitation programs have been demonstrated to increase claudication distance in patients with PAD through improvements in peripheral circulation, walking economy, and cardiopulmonary function (71). The optimal exercise program for improving claudication pain distance in persons with PAD uses intermittent walking to near-maximal pain during a program of at least 6 months (72). Strength training is less effective than treadmill walking (73).

LOWER EXTREMITY ANGIOPLASTY AND BYPASS SURGERY

Table 4 shows that the indications for lower extremity percutaneous transluminal angioplasty or bypass surgery are 1) incapacitating claudication in persons interfering with work or lifestyle; 2) limb salvage in persons with limb-threatening ischemia as manifested by rest pain, nonhealing ulcers, and/or infection or gangrene; and 3) vasculogenic impotence (74). Percutaneous transluminal angioplasty can be performed if there is a skilled vascular interventionalist and the arterial disease is localized to a vessel segment less than 10 cm in length (74). Compared to percutaneous transluminal angioplasty alone, stenting improves 3-year patency by 26% (75).

AMPUTATION

Nonrandomized studies have shown that both immediate and long-term survival is higher in patients having revascularization rather than amputation for limb-threatening ischemia (76,77). However, amputation of lower extremities
should be performed if tissue loss has progressed beyond the point of salvage, if surgery is too risky, if life expectancy is very low, or if functional limitations obviate the benefit of limb salvage (78).

ACKNOWLEDGMENT
Address correspondence to Wilbert S. Aronow, MD, FGSA, Cardiology Division, New York Medical College, Macy Pavilion, Room 138, Valhalla, NY 10595. E-mail: WSAronow@aol.com

REFERENCES


52. Aronow WS, Ahn C. Elderly diabetics with peripheral arterial disease and no coronary artery disease have a higher incidence of new coronary events than elderly nondiabetics with peripheral arterial disease and prior myocardial infarction treated with statins and with no lipid-lowering drug. J Gerontol Med Sci. 2003;58A:573–575.


55. Ghosh S, Aronow WS. Utilization of lipid-lowering drugs in elderly persons with increased serum low-density lipoprotein cholesterol associated with coronary artery disease, symptomatic peripheral arterial disease, prior stroke, or diabetes mellitus before and after an educational program to treat dyslipidemia. J Gerontol Med Sci. 2003;58A:M432–M435.


