

Peripheral Vascular Disease: Diagnosis and Treatment

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Peripheral vascular disease is a manifestation of systemic atherosclerosis that leads to significant narrowing of arteries distal to the arch of the aorta. The most common symptom of peripheral vascular disease is intermittent claudication. At other times, peripheral vascular disease leads to acute or critical limb ischemia. Intermittent claudication manifests as pain in the muscles of the legs with exercise; it is experienced by 2 percent of persons older than 65 years. Physical findings include abnormal pedal pulses, femoral artery bruit, delayed venous filling time, cool skin, and abnormal skin color. Most patients present with subtle findings and lack classic symptoms, which makes the diagnosis difficult. The standard office-based test to determine the presence of peripheral vascular disease is calculation of the ankle-brachial index. Magnetic resonance arteriography, duplex scanning, and hemodynamic localization are noninvasive methods for lesion localization and may be helpful when symptoms or findings do not correlate with the ankle-brachial index. Contrast arteriography is used for definitive localization before intervention. Treatment is divided into lifestyle, medical, and surgical therapies. Lifestyle therapies focus on exercise, smoking cessation, and dietary modification. Medical therapy is directed at reducing platelet aggregation. In addition, patients with contributing disorders such as hypertension, diabetes, and hyperlipidemia need to have these conditions managed as aggressively as possible. Surgical therapies include stents, arterectomies, angioplasty, and bypass surgery. (*Am Fam Physician* 2006;73:1971-6. Copyright © 2006 American Academy of Family Physicians.)

► **Patient information:**
A handout on peripheral arterial disease and claudication is available at: <http://familydoctor.org/008.xml>.

Peripheral vascular disease (PVD) is the presence of systemic atherosclerosis in arteries distal to the arch of the aorta. As a result of the atherosclerotic process, patients with PVD develop narrowing of these arteries. The most common symptom of PVD is intermittent claudication, which manifests as pain in the muscles of the legs with exercise and is experienced by 2 percent of persons older than 65 years.¹ In one study of outpatients in the United States, PVD was present in 29 percent of patients.² This study included patients older than 70 and patients 50 to 69 years of age with a history of cigarette smoking or diabetes mellitus. The greatest modifiable risk factor for the development and progression of PVD is cigarette smoking. Cigarette smoking increases the odds for PVD by 1.4 for every 10 cigarettes smoked per day.³

Screening and Primary Prevention

To date, no studies have attempted to document reductions in morbidity and mortality that result from screening for PVD in primary

care. The U.S. Preventive Services Task Force has recommended against routine screening for peripheral arterial disease.⁴

Primary prevention of PVD consists of encouraging smoking cessation. Smoking cessation also is recommended for the prevention of coronary artery disease, chronic obstructive pulmonary disease, stroke, and lung cancer.

Diagnosis

The differential diagnosis of PVD includes musculoskeletal and neurologic causes. The most common entity that mimics PVD is spinal stenosis. Spinal stenosis can cause compression of the cauda equina, which results in pain that radiates down both legs. The pain occurs with walking (i.e., pseudoclaudication) or prolonged standing and does not subside rapidly with rest. Additional conditions to consider are acute embolism, deep or superficial venous thrombosis, restless legs syndrome, systemic vasculitides, nocturnal leg cramps, muscle or tendon strains, peripheral neuropathy, and arthritides (*Table 1*).⁵

SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>
The most reliable physical findings of PVD are diminished or absent pedal pulses, presence of femoral artery bruit, abnormal skin color, and cool skin temperature.	B	10
The laboratory work-up at time of diagnosis should include a complete blood count with platelet count, fasting glucose or A1C, fasting lipid profile, serum creatinine, and urinalysis for glucosuria and proteinuria.	C	12
Duplex ultrasonography, magnetic resonance arteriography, and angiography are indicated for determining lesion localization in PVD and are best used when invasive or surgical intervention is a possibility.	C	13
Exercise has been shown to increase the walking time of patients with claudication by 150 percent (i.e., 6.51 minutes).	A	16
Aspirin reduces risk of serious vascular events in patients with PVD, with doses of 75 to 150 mg being as effective as higher doses.	A	17
Patients with PVD and hypercholesterolemia should be treated with appropriate dietary modification and lipid-lowering agents, as needed.	B	22, 23
Aggressive blood pressure reduction should be pursued in patients with PVD.	C	24

PVD = peripheral vascular disease.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 1874 or <http://www.aafp.org/afpsort.xml>.

**TABLE 1
Differential Diagnosis of Claudication**

<i>Condition</i>	<i>Pain location</i>	<i>Characteristics of pain</i>	<i>Does exercise cause pain?</i>	<i>Effect of rest on pain</i>
Baker cyst, symptomatic	Behind knee and down calf	Tender to touch, associated swelling	Yes	None; pain is present at rest
Calf claudication	Calf muscles	Cramping	Yes	Subsides quickly
Chronic compartment syndrome	Calf muscles	Tight, throbbing	Yes	Subsides slowly
Foot arthritis	Foot and arch	Aching	Yes, with varying degree	Subsides slowly
Foot claudication	Foot and arch	Severe, deep; associated numbness	Yes	Subsides quickly
Hip arthritis	Hip, thigh, and gluteal region	Aching	Yes, with varying degree	Subsides slowly
Hip claudication	Hip, thigh, and gluteal region	Aching, associated weakness	Yes	Subsides quickly
Nerve root compression	Down one leg and posterior	Sharp, stabbing	Yes, almost immediately	Subsides slowly
Spinal stenosis	Hip, thigh, and gluteal region	Some pain, but weakness predominates	Yes, after some time, includes standing	Subsides after some time; accompanied by position change (e.g., sitting down)
Venous claudication	Entire leg, but worse in thigh and groin	Tight, throbbing	Yes	Subsides slowly

Adapted with permission from Dormandy JA, Rutherford RB. TASC Working Group. Management of peripheral arterial disease (PAD). TransAtlantic Inter-Society Consensus (TASC). J Vasc Surg 2000;31(1 pt 2):S1-S296.

TABLE 2
Edinburgh Claudication Questionnaire

Question	Response	Sensitivity (%)	Specificity (%)
Do you get pain or discomfort in your leg(s) when you walk?	Yes (If patient answers no, then stop here)	99.3	13.1
Does this pain ever begin when you are standing still or sitting?	No	99.3	80.3
Do you get pain if you walk uphill or hurry?	Yes	98.8	13.1
Do you get pain if you walk at an ordinary pace on level ground?	Yes or no, dependent on severity of claudication	—	—
What happens if you stand still?	Pain gone in 10 minutes or less	90.6	63.9
Where do you get this pain?	Calf,* thigh, or buttock† marked	—	—

NOTE: A positive classification for peripheral vascular disease requires the indicated responses for all questions.

*—Definite claudicant = pain in calf.

†—Atypical claudication = pain in thigh or buttock (in the absence of calf pain).

Adapted with permission from Leng GC, Fowkes FG. The Edinburgh Claudication Questionnaire: an improved version of the WHO/Rose Questionnaire for use in epidemiological surveys. *J Clin Epidemiol* 1992;45:1104.

Effect of body position on pain	Other comments
None	Constant
None	Reproducible
Subsides more quickly with elevation	Common in heavily muscled athletes
Aided by not bearing weight	Varies, may relate more to activity level or weather changes
None	Reproducible
More comfortable sitting	Varies, may relate more to activity level or weather changes
None	Reproducible
Usually relieved by changing position	History of back problems
Relieved by lumbar spine flexion	History of back problems
Subsides more quickly with elevation	History of iliofemoral deep venous thrombosis, signs of venous congestion and edema

Patients with PVD have a history of claudication, which manifests as cramp-like muscle pain occurring with exercise and subsiding rapidly with rest. In addition, later in the course of the disease, patients may present with night pain, nonhealing ulcers, and skin color changes. However, PVD is asymptomatic in almost 90 percent of patients.² The Edinburgh Claudication Questionnaire has been shown to be 91 percent specific and 99 percent sensitive for diagnosing intermittent claudication in symptomatic patients.⁶ It is composed of a series of six questions and a pain diagram that are self-administered by the patient (*Table 2*).⁶

Classic risk factors for PVD are smoking, diabetes mellitus, hypertension, and hyperlipidemia. Recent trials have added chronic renal insufficiency,⁷ elevated C-reactive protein levels,⁸ and hyperhomocysteinemia⁹ to the list of risk factors. In one series from the Netherlands, the likelihood of a patient having PVD (as defined by an ankle-brachial index [ABI] of less than 0.9) was increased by being male (odds ratio [OR] 1.6); being older than 60 years (OR 4.1); having hypercholesterolemia (OR 1.9); having a history of ischemic heart disease (OR 3.5), cerebrovascular disease (OR 3.6), diabetes mellitus (OR 2.5), or intermittent claudication (OR 5.6); or smoking (OR 1.6).⁹

Physical examination findings in patients with PVD vary. They may include absent or diminished pulses, abnormal skin color, poor hair growth, and cool skin. The most reliable physical findings are diminished or absent pedal pulses, presence of femoral artery bruit, abnormal skin color, and cool skin (*Table 3*¹⁰), but their absence does not preclude PVD.

TABLE 3
Physical Findings for PVD with Sensitivity, Specificity, and Likelihood Ratios

Finding	Description	ABI	Sensitivity (%)	Specificity (%)	LR+
Abnormal pedal pulse	DP and PT pulses absent	< 0.9	63	99	44.6
	PT and DP pulses absent or one absent and one weak	< 0.9	73	92	9.0
Femoral artery bruit	Bruit present	< 0.8	20	96	4.7
	Bruit present	< 0.9	29	95	5.7
Cool skin	Unilateral cooler skin	< 0.9	10	98	5.8
Abnormal color	Pale, red, or blue	< 0.9	35	87	2.8

PVD = peripheral vascular disease; ABI = ankle-brachial index; LR+ = positive likelihood ratio; DP = dorsalis pedis; PT = posterior tibial.

Adapted with permission from McGee SR, Boyko EJ. Physical examination and chronic lower-extremity ischemia: a critical review. *Arch Intern Med* 1998;158:1360.

Once PVD is suspected, physicians can screen patients using ABI testing on one or both extremities. The presence of an ABI less than 0.9 is consistent with PVD. The ABI will not exclude proximal aneurysms or arterial disease distal to the ankle.¹¹ ABI testing, which requires a blood pressure cuff and a Doppler device with a probe for detecting arterial pulses, may be performed in the office or hospital setting. Laboratory studies to be ordered at the time of diagnosis include complete blood count with platelet count, fasting glucose or A1C, fasting lipid profile, serum creatinine, and urinalysis for glucosuria and proteinuria.¹² Further laboratory studies, including those for coagulopathies, are reserved for atypical situations.¹² Although elevated homocysteine, C-reactive protein, and lipoprotein A levels are risk factors for PVD, there are no outcomes studies to demonstrate that lowering these levels leads to clinical benefit for patients with PVD. Additional studies such as duplex ultrasonography, magnetic resonance arteriography, and angiography are indicated for determining lesion localization and are best used when invasive or surgical intervention is a possibility.¹³

PVD can be managed by monitoring degree of pain, pain-free walking distance, and other areas in which PVD affects patients' lives. Changes in functional status may prompt the physician to repeat ABI testing, order further testing, or refer the patient to a vascular subspecialist.

Patients with claudication may progress to acute or critical limb ischemia, although the risk is less than 1 percent per year.¹⁴ Acute limb ischemia is indicated by the abrupt onset of pain, pulselessness, pallor, paresthesia, and paralysis in the affected limb (Table 4⁵) and requires acute intervention. Critical limb ischemia

is the progression of symptoms to the point that rest and night pains are present. These symptoms mark ongoing ischemia and necessitate intervention.

Treatment

Treating patients with PVD requires addressing each risk factor that led to the development of PVD. Permanent abstinence from cigarette smoking is the most important factor related to outcomes in patients with intermittent claudication.^{13,15} Exercise has been shown to increase the walking time of patients with claudication by 150 percent (i.e., 6.51 minutes) in those who comply with the regimen.¹⁶

Drug therapy for patients with PVD includes several options. In a recent meta-analysis,¹⁷ antiplatelet therapy was evaluated for risk reduction in serious vascular events including stroke, nonfatal myocardial infarction, or death from a vascular cause. Among patients

TABLE 4
Differential Diagnosis of Acute Limb Ischemia

Condition	Characteristics
CHF, superimposed on chronic arterial disease	History of CHF; severe low output state leads to lack of pulse and to classic findings of pain, pallor, paresthesia, and paralysis similar to acute limb ischemia; angiography does not show occlusion.
Deep venous thrombosis, acute (phlegmasia cerulea dolens)	Presents as a large, swollen, and painful leg, which appears blue because of incipient venous infarction; pallor is not present; results from extensive thrombotic occlusion of the iliofemoral veins; pulses may be absent.
Acute spinal cord compression	Pain, paresthesia, and paralysis present; normal skin color and pulse

CHF = congestive heart failure.
 Information from reference 5.

with PVD, antiplatelet therapy was associated with an absolute risk reduction of 22 events per 1,000 patients treated for two years (number needed to treat = 45). Aspirin was most commonly studied in this analysis, with dosages of 75 to 150 mg per day being as effective as higher dosages. The Clopidogrel versus Aspirin in Patients at Risk for Ischemic Events (CAPRIE) trial¹⁸ showed that clopidogrel (Plavix) is equally effective compared with aspirin and possibly more so when patients with PVD are subgrouped. This finding must be taken with caution, however, because the CAPRIE trial was not designed for subgroup analysis. Most current approaches recommend aspirin first and then clopidogrel for patients who are intolerant of aspirin or who continue to have events while taking aspirin.¹³ The combination of aspirin and clopidogrel for PVD has not been studied in a clinical trial.

Cilostazol (Pletal) is a vasodilator with antiplatelet properties. It has been shown to increase walking distance by 35 to 109 percent in several randomized, blinded trials,¹⁹⁻²¹ but it has never been compared with exercise in a trial. Pentoxifylline (Trental) is a rheologic modulator that also has antiplatelet effects. It is approved by the U.S. Food and Drug Administration for the treatment of intermittent claudication. However, critical reviews^{20,21} have found limited evidence of effectiveness, which the authors believed was insufficient to recommend routine use in treating PVD.

Addressing any comorbidity that affects the course of PVD is essential to its treatment. Hypercholesterolemia clearly is related to atherosclerotic disease. One systematic review²² and a recent clinical trial²³ have shown lipid lowering to be beneficial for patients with PVD; however, a variety of outcomes were used and the generalizability of these findings remains an issue until clear patient-oriented trials are conducted. Considering the number of patients with conditions that merit lipid-lowering therapy, patients with PVD and hypercholesterolemia should be treated with appropriate dietary modification and lipid-lowering agents, if needed.

When hypertension and type 2 diabetes are present with PVD, one trial²⁴ has shown that aggressive blood pressure reduction reduces cardiovascular events, although only 53 patients were followed for four years and this is a subgroup analysis. In this study, blood pressure was lowered to a mean of 128/75 mm Hg, approximating the American Diabetes Association standard of blood pressure treatment in patients who have diabetes to a goal of less than 130/80 mm Hg.²⁵ The Heart Outcomes Prevention Evaluation (HOPE) trial demonstrated that ramipril (Altace), an angiotensin-converting enzyme

(ACE) inhibitor, reduced cardiovascular morbidity and mortality in patients with PVD by 25 percent.^{26,27} Patients did not have to be hypertensive in the HOPE trial, and the reduction in morbidity and mortality was beyond what was expected for the amount of blood pressure reduction.

If these results can be replicated, most patients with PVD would benefit from ramipril or any ACE inhibitor shown to have this effect, provided the physician monitors

serum creatinine levels for deterioration when occult renal artery stenosis is present. Anticoagulants (i.e., heparin, warfarin [Coumadin], low-molecular-weight heparin) have not shown any benefit in treating patients with intermittent claudication.²⁸ Heparin has been shown to be beneficial in reducing morbidity and mortality in patients with acute limb ischemia while they are being evaluated for further treatment.¹²

Beyond medical therapy for intermittent claudication, patients who progress to critical or acute limb ischemia face several treatment options. These include endovascular stenting, intra-arterial thrombolytic drugs (urokinase [Abbokinase]), angioplasty, angioplasty combined with brachytherapy (i.e., delivery of radiation to peripheral arteries through local catheters intended to reduce restenosis following percutaneous transluminal angioplasty), and bypass grafting. To date, there are no firm evidence-based criteria for deciding which patients will benefit from a given procedure. Factors to be considered in such situations are location of lesion, patient-related risks, surgery-related risks, type of clot, and contraindications to thrombolysis.¹² Antiplatelet therapy is recommended for patients who have undergone bypass grafting.¹² One agent, ticlopidine (Ticlid), demonstrated increased saphenous graft patency in patients who were followed for two years after surgery.²⁹

Prognosis

Several studies have demonstrated that patients with PVD have higher mortality rates than those in the control groups. One study³⁰ showed an all cause mortality rate of 3.8 percent per year for patients with PVD and claudication, 6.1 percent for patients with PVD and no symptoms, and 2.0 percent per year in the control group. This study included 1,592 patients (men and women) from Scotland who were followed prospectively for five

Acute limb ischemia is heralded by the abrupt onset of pain, pulselessness, pallor, paresthesia, and paralysis in the affected limb and requires acute intervention.

years and highlights the risk found in patients with PVD. Unfortunately, there are no data to demonstrate that early identification of patients with PVD is beneficial in terms of mortality or morbidity reduction.

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