

Screening and Basic Workup of a Patient with Peripheral Vascular Disease – A Primer of Physicians

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Abstract

Peripheral vascular disease (PVD) is a prevalent condition associated with significant morbidity and mortality in a variety of patient populations. When not properly recognized and treated, it can result in complications that include myocardial infarction, ischemic stroke, and cardiovascular death. In this review, we describe the risk factors, clinical presentation, diagnostic evaluation, treatment, and alternative diagnoses that can confound the diagnosis of PVD.

Keywords: Peripheral vascular disease; PVD; Peripheral Arterial Disease; PAD

Introduction

Peripheral artery disease (PAD) is as a narrowing or obstruction of at least one peripheral artery that compromises circulation. Obstruction occurs via deposition of lipid and fibrotic material between the intimal and medial layers of vessels. This results in plaque formation [1]. Plaques most commonly form in the distal superficial femoral and proximal popliteal arteries; areas commonly responsible for calf muscle claudication [2]. PAD may also be caused by thrombotic events, which occur rapidly and cause acute limb ischemia [3].

PAD affects more than 200 million people worldwide and is more prevalent in lower socioeconomic demographics. From 2000-2010, the prevalence in low and middle-income regions has increased 29%, and in high-income regions 13% [4]. In the United States, there are approximately 8.5 million people with PAD. PAD is more prevalent in high-income countries than low-income countries, specifically in older age groups, which is likely a function of increased survival times with co-morbid conditions [4]. PAD is also more prevalent in African American and Hispanic communities but equally prevalent in both men and women [5].

There is significant morbidity and mortality associated with PAD. PAD is strong independent risk factor of cardiovascular and cerebrovascular disease [6]. The 1-year incidence of cardiovascular death, myocardial infarction (MI), and ischemic stroke has been shown to be higher in PAD than in coronary heart disease [7]. The incidence of adverse limb outcomes, including worsening of symptoms, need for revascularization, and amputation was also found to be 26% over a 4-year period [8]. In the elderly, PAD has costs Medicare approximately \$4.37 billion [9].

Risk Factors

The American College of Cardiology/American Heart Association (ACC/AHA) guidelines indicate the following groups are risk factors for PAD [10]:

- Patients older than 70 years
- Patients 50-69 years with a history of smoking or diabetes
- Patients 40-49 years with diabetes and at least one other risk factor for atherosclerosis, leg symptoms suggestive of claudication with exertion or ischemic pain at rest, abnormal lower extremity pulse examination, or known atherosclerosis disease

Smoking and diabetes are the strongest risk factors for PAD [4]. Markers of inflammation, and thrombosis, elevated lipoprotein(a) and homocysteine levels, and chronic kidney disease are also associated with peripheral arterial disease [11]. Men are more likely than women to have symptoms of claudication, though the prevalence of PAD among men and postmenopausal women is similar [12]. There is also a heritable component to PAD, and a positive family history may double the risk of susceptibility to PAD [13,14].

Clinical Presentation and Diagnostic Evaluation

Clinical presentation of PAD ranges from asymptomatic to threatened limb based on the degree of obstruction, number of arteries involved, and the activity level of the patients. The Rutherford Classification is the most commonly used system to classify acute and chronic limb ischemia. It incorporates clinical symptoms with objective findings, including Doppler, ABI (ankle-brachial index), and pulse volume recordings. ABI is the ratio of blood pressure at the ankle to upper arm and can help identify arterial occlusion from PAD, as described in a subsequent section. The chronic limb ischemia classification resembles Fontaine's classification with the addition of objective, noninvasive data. The acute limb ischemia classification divides an extremity into viable, threatened, or irreversibly damaged categories. The chronic and acute Rutherford Classifications are found in Tables 1 and 2, respectively [15-17].

Grade	Category	Clinical Description	Objective Criteria
0	0	Asymptomatic – no hemodynamically significant occlusive disease	Normal treadmill or reactive hyperemia test
I	1	Mild claudication	Completes treadmill exercise; AP after exercise > 50 mmHg but at least 20 mmHg lower than resting value
	2	Moderate claudication	Between categories 1 and 3
II	3	Severe claudication	Cannot complete standard treadmill exercise, and AP after exercise < 50 mmHg
	4	Ischemic rest pain	Resting AP < 40 mmHg, flat or barely pulsatile ankle or metatarsal PVR; TP < 30 mmHg
III	5	Minor tissue loss – nonhealing ulcer, focal gangrene with diffuse pedal ischemia	Resting AP < 60 mmHg, ankle or metatarsal PVR flat or barely pulsatile; TP < 40 mmHg
	6	Major tissue loss – extending above TM level, functional foot no longer salvageable	Same as category 5

List of Abbreviations: AP: Ankle Pressure; PVR: Pulse Volume Recording; TM: Transmetatarsal; TP: Toe Pressure
Table 1: Rutherford Classification for Chronic Limb Ischemia

Category	Description/Prognosis	Findings		Doppler Signal	
		Sensory Loss	Muscle Weakness	Arterial	Venous
I. Viable	Not immediately threatened	None	None	Audible	Audible
Ia. Threatened Marginally	Salvageable if promptly treated	Minimal (toes) or none	None	Inaudible	Audible
Ib. Threatened Immediately	Salvageable with immediate revascularization	More than toes, associated rest pain	Mild, moderate	Inaudible	Audible
III. Irreversible	Major tissue loss or permanent nerve damage inevitable	Profound, anesthetic	Profound, paralysis	Inaudible	Inaudible

Table 2: Rutherford Classification for Acute Limb Ischemia

Asymptomatic PAD is usually suspected during physical examination significant for decreased pedal pulses. Approximately 20-50% of patient >50 years old with PAD have asymptomatic presentation [18]. Intermittent claudication or classic claudication is defined as discomfort of a group of muscles, typically calf muscles, on exertion. It is alleviated by a few minutes of rest and usually represents 10-35% of patients with PAD.

Atypical leg pain is more common than classic claudication in those with low levels of activity and those with different perceptions of pain. Atypical claudication accounts for approximately 40-50% of patients with PAD [19]. Acute/chronic limb ischemia represents a minimal percentage of the PAD population. Even though the incidence rate is low compared to the other classifications, it is the most severe and life threatening. Based on 2007 TASC II, if limb ischemia caused by an abrupt obstruction of perfusion by a thrombus presents within two weeks, it is considered acute. Similar presentations associated with rest limb pain and pulseless, with an onset lasting more than two weeks are considered chronic [20]. Skin temperature is an indicator of blood flow rate and can be useful as a marker of perfusion. Ischemic limbs are cool, and demarcation of temperature change can give rough indication of the level of occlusion.

Patients with PAD usually suffer from atherosclerotic disease in other vascular beds such as the coronary, carotid, and renal arteries. When PAD is suspected, the workup should include an ECG to assess for prior cardiac injury. CBC, standard chemistry, PT/PTT, and CPK should also be evaluated to assess for end-organ injury and factors that might contribute to a decrease in peripheral perfusion. There has been strong evidence suggesting a prothrombotic state in atherosclerotic disease. Therefore, anticardiolipin antibodies, homocysteine levels and PF4 antibodies should be evaluated. Elevated urinary leukotriene E₄ has been

observed in patients with restenosis and reocclusion after percutaneous transluminal angioplasty, and serial measurements may predict clinical manifestations in the months prior to symptom onset [21].

Questionnaires, including the Rose/WHO Questionnaire, Edinburgh Claudication Questionnaire, and San Diego Claudication Questionnaire, have been used extensively to assess the presence of claudication and detect the presence of PAD. Although often highly specific, they are relatively insensitive for the detection and diagnosis of PAD [22]. Other questionnaires, which include the Walking Impairment Questionnaire, the Short-Form-36 Physical Functioning Score, Peripheral Artery Questionnaire, and the PAD Quality of Life Questionnaire, are validated questionnaires that can help assess change in patient-reported walking performance and quality of life. The outcomes of these questionnaires are not interchangeable. Each outcome measures a different aspect of walking performance or quality of life, and should therefore be used in conjunction with other subjective and objective data to determine management [23].

A very detailed physical exam is necessary to diagnose or have a high suspicion for compromised peripheral circulation. Physical findings such as non-healing wound, skin discoloration and gangrene, rest pain, claudication, or decreased pedal pulses in addition to positive risk factors for atherosclerotic disease should trigger a workup for PAD. The resting ABI is the initial diagnostic test and is usually the only test needed in order to establish the diagnosis of PAD. The test measures the ratio of the systolic blood pressures at the lower (dorsalis pedis and posterior tibial) and upper (brachial) arteries in a supine position using a doppler sonography [24]. The classification is as follows: <0.9 is abnormal; a 0.91-0.99 is borderline; 1.00-1.40 is normal; >1.40 is not compressible. In the setting of a symptomatic patient with a normal or borderline resting ABI, additional testing is indicated, including exercise treadmill ABI to assess functional status.

There are two types of exercise treadmill testing: constant-loading testing and graded testing. Constant-load testing is performed at a single work rate and grade, whereas graded testing increases intensity a regular time intervals. The goal is to push patients to their maximally tolerated pain that results in an inability to walk any further. Constant-load protocols may be limited in that some patients with mild PAD may be able to walk for extended periods of time without claudication symptoms [25]. In contrast, graded treadmill testing has a large dynamic range that can reproducibly define a patient's peak PAD-limited peak walking and claudication onset time [26]. The 6-minute walking can also be used to evaluate functional status in PAD, though data supporting its use in PAD is less extensive than for graded exercise treadmill testing [25]. Nevertheless, the 6-minute walking test may more directly measure outcomes that are relevant to daily function and quality of life than treadmill testing [27].

Toe-brachial index (TBI) is the ratio between the toe pressure and the higher of the two brachial pressures. It is typically used in patients who are expected to have vessel stiffness, such as those with diabetes, chronic kidney disease or advanced age. It is also used in patients who have elevated ABIs [28,29]. The diagnostic criteria for normal vs. pathologic TBI remains ambiguous, but several guidelines and reviews recommend <0.70 be used as a cutoff [10,20,30-34].

Other means of non-invasive hemodynamic assessment of PAD in the lower limbs include near infrared spectroscopy (NIRS) and measurement of transcutaneous partial pressure of oxygen (TcPO₂). NIRS can be used during a treadmill test or during a toe flexion test in patients unable to walk to objectively define PAD presence or severity and foot perfusion [35]. TcPO₂ can provide evidence of exercise-induced regional blood flow impairment during both exercise and recovery [36,37]. Normal TcPO₂ levels are approximately 60mmHg. Levels of 20 mmHg or less are indicative of severely reduced blood flow and indicate revascularization is required. More liberal use of TcPO₂ should be considered in diabetics as they may be asymptomatic, often due to neuropathy and lack of activity, but have significant PAD [38].

Computed tomographic angiography (CTA) and magnetic resonance angiography (MRA) are useful to diagnose anatomic location and degree of stenosis in patients with symptomatic PAD in whom revascularization is being considered. If CT or MRA are not possible or the results are insufficient for making a decision on revascularization, invasive angiography may be considered [39]. CT angiography is widely available, requires a short scanning time, and provides high-resolution images that can be three-dimensionally reconstructed. It does, however, require vascular contrast and may not provide delineation of heavily calcified or small distal vessels. MRA does not use radiation and also provides good spatial resolution but is technically more challenging than CT angiography, cannot be used in patients with certain metallic or electronic implants, and carries a risk of nephrogenic systemic fibrosis when gadolinium is used in patients with CKD [12].

According to the ACC/AHA 2005 Practice Guidelines, subjects with claudication should be screened using Doppler ultrasonography (US). Doppler US can be used for the determination of anatomic localization, grade of stenosis, and for follow-up of post-operative femoropopliteal and femorotibial-pedal vein grafts. Doppler US is also recommended for selection of subjects that could benefit from endovascular intervention and for follow-up after endovascular treatment. With respect to revascularization surgery, doppler US can identify the level of arterial segments that require surgical anastomoses, however its utility, in the identifying long-term success of percutaneous transluminal angioplasty is not clear [40,41].

Treatment

Management of patients with PAD should include an exercise program, medical therapy to reduce cardiovascular risk, and when indicated, revascularization [42]. In patients with PAD and no other cardiovascular disease, the use of multiple preventative therapies was associated with a 65% lower all-cause mortality (HR: 0.35, p=0.02) [43]. The American College of Cardiology

Foundation (ACCF) and American Heart Association (AHA) guidelines also suggest a multi-disciplined approach to treating lower extremity PAD, which includes smoking cessation, lipid lowering therapy, diabetes and hypertension control, and exercise therapy [10].

Exercise

The goal of an exercise regimen in those physically limited secondary to PAD is to improve functional status and quality of life. Physical activity in patients with PAD is associated with decreased all-cause and cardiovascular mortality [44,45]. 12-week supervised exercise programs have been shown to improve exercise performance and quality of life in PAD [46]. They are also more cost-effective than endovascular revascularization, as is a stepped approach of exercise therapy followed by endovascular revascularization than revascularization alone [48,47]. Supervised exercise in a hospital or outpatient facility is recommended for all patients with PAD [49]. Structured or home-based exercise may be considered as an alternative treatment modality as it has not been shown as efficacious as supervised exercise [50]. Generally, an exercise regimen should include treadmill exercise training for 45 minutes, 3-5 days per week. Patients should increase workload as able, stopping when symptoms reach a mild-moderate discomfort level and resuming when symptoms are relieved [51,52]. Nordic walking (NW) exercises may also be recommended, as they have been shown to increase walking distance in patients with PAD [53,54]. They involve a 10-minute warm-up, a 45-minute session of walking at a pace dictated by a calculated training heart rate, and a 5-minute low-intensity cool down 5 times per week for 2 months [55].

Smoking Cessation

Smoking cessation is one of the most important lifestyle modifications to prevent chronic limb ischemia, amputation, and major adverse cardiac events in patients with PAD [42]. Tobacco cessation has been shown to lower 5-year mortality and improve amputation-free survival [56]. Cessation should be encouraged at every office visit.

Diet Modification

Improper nutrient intake has been shown to contribute to the development and progression of PAD [57-62]. The 2013 AHA/ACC Guidelines broadly emphasize diets rich in fruits, vegetables, whole grains, legumes, as well as limiting calories from saturated fats to no more than 5-6% of total calorie intake, reducing dietary monounsaturated fats, and minimizing intake of foods rich in trans-fats, which are commonly found in milk, animal fats, and some vegetable oils. The Dietary Approaches to Stop Hypertension (DASH) diet is the only diet to hold a class IA recommendation for primary and secondary prevention of cardiovascular disease and should be recommended to all patients with PAD [63]. The Mediterranean diet is another reasonable alternative.

Diabetes Treatment

Treatment of diabetes does not reduce the risk of cardiovascular events, but it may lower the risks of neuropathy and microvascular disease [64]. This recommendation applies to patients with PAD and diabetes at risk for debilitating foot ulceration. Glycemic goals should be based on age, duration of diabetes, and relevant comorbidities rather than tight glycemic control, which may increase mortality among patients with cardiovascular disease [65]. Proper foot care and daily foot inspections are also recommended.

Cilostazol

Cilostazol should be considered in patients with intermittent claudication refractory to exercise therapy and smoking cessation. It may be used in combination with either aspirin or clopidogrel but is contraindicated in patients with heart failure. Cilostazol has been shown to increase maximal and pain-free walking distances in patients with moderate-severe claudication [66]. This benefit, however, may take up to 4 months to become apparent [67]. Although it appears to be safe long-term, adherence is low due to side effects which include headache, palpitations, and diarrhea [67].

ACE Inhibitors

ACE inhibitors (ACEIs) should be considered in both symptomatic and asymptomatic patients with lower extremity PAD to reduce the risk of adverse cardiovascular events [10]. Data for their use derives from the HOPE trial, which evaluated the role of ramipril in patients who were at high risk for cardiovascular events that did not have left ventricular dysfunction or heart failure [68]. The study found significant reductions in rates of death, myocardial function, and stroke. ACEIs also reduce blood pressure, and while one trial suggested systolic blood pressure goals of less than 120 mmHg, blood pressure targets remain a controversial issue [12,69].

Statins

High-intensity statins are indicated in PAD to reduce the risk of cardiovascular disease. Treatment should be based on cardiovascular risk rather than low-density lipoprotein targets [70]. Data for their use derives mostly from the Heart Protection Study (HPS), which showed reduction in first major vascular (MI, coronary death, stroke, or revascularization) and PAD events [71]. Statins have also been shown to reduce in adverse limb outcomes including amputation and are associated with combined endpoint reductions in worsening claudication, new CLI, and/or new revascularization [72,73].

Antiplatelet Agents

The 2005 and 2011 ACCF/AHA Guidelines recommend aspirin for patients with symptomatic PAD (IA recommendation), and asymptomatic patients with PAD and either an ABI < 0.9 (IIA recommendation) or ABI of 0.9-0.99 (IIB recommendation) [10]. Recent data from the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) and Aspirin for Asymptomatic Atherosclerosis (AAA) trials, however, showed no reduction in fatal and nonfatal cardiovascular events or revascularization with aspirin monotherapy [74,75]. These guidelines may change with future revisions, so their use should be at the discretion of the clinician, taking other co-morbidities into account [42]. Vorapaxar is another antiplatelet medication that can be considered in patients with PAD without a history of stroke. Vorapaxar was shown to reduce the risk of cardiovascular death or ischemic events in patients with atherosclerotic vascular disease [76]. In a subgroup of patients with PAD, it also reduced the risk of acute limb ischemia and peripheral-revascularization events [77]. Vorapaxar is contraindicated in patients with a history stroke because of its increased risk of bleeding, specifically intracranial hemorrhage.

Clopidogrel

Clopidogrel can be considered for both monotherapy and dual-antiplatelet therapy (DAPT) in patients with PAD. The Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial showed benefit in long-term administration of clopidogrel to patients with atherosclerotic vascular disease reduces risk of ischemic stroke, MI, or vascular death when compared with aspirin [78]. Data for DAPT has been mixed and is most commonly used after endovascular intervention. A propensity-matched observational study among patients undergoing endovascular intervention showed a significant reduction in MACE among patients taking DAPT versus aspirin monotherapy [79]. Other trials, such as the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) and Clopidogrel and Acetylsalicylic Acid in Bypass Surgery for Peripheral Artery Disease (CASPAR) trials showed no overall significant benefit from daily aspirin and clopidogrel when compared to daily clopidogrel use [80,81].

Revascularization Therapy

Revascularization therapy should be considered in symptomatic patients with a reasonable likelihood of symptom reduction despite optimal pharmacological therapy and exercise program participation. Revascularization is also indicated for limb salvage in critical limb ischemia (CLI) [12]. Generally, if a patient is a candidate for both endovascular and open surgery, the less-invasive endovascular option is preferred [42]. The goal of revascularization in claudication is relief of symptoms. The goal in CLI is rapid reperfusion of ischemic tissue to prevent amputation and restore ambulation [42].

Endovascular-first approaches are recommended for aortoiliac lesions, femoral-popliteal lesions, infrapopliteal lesions, and CLI [10,82]. In aortoiliac and femoral-popliteal disease, endovascular intervention is preferred due to high procedural success rates and low risk [82]. In common femoral disease, endarterectomy has traditionally been used, but there is data to suggest endovascular interventions have high success rates [42,83]. Endovascular therapy in infrapopliteal disease has a low rate of periprocedural events, with mortality rates in observational series <1% [42]. Surgical bypass should be considered when endovascular therapy is unsuccessful or is not feasible from an anatomical standpoint, including attempts at retrograde percutaneous angioplasty if intergrade access recanalization is not possible [12].

Other Differential Diagnoses

PAD should not be confused with other diagnoses that it symptomatically mimics. Described below are contrasts between PAD and other common disease processes.

Spinal Canal Stenosis

Spinal canal stenosis may resemble PAD when there is lumbar involvement due to weakness, pain, and numbness of the legs. The symptoms of lumbar stenosis may be worse with ambulation, present bilaterally, and can present as intermittent, crampy pain that can resemble PAD. Unlike PAD however, lumbar stenosis is exacerbated by standing erect and alleviated by laying supine. The symptoms of PAD will remain unchanged during flexion and extension of the spine. Lumbar stenosis is not exacerbated with biking or uphill ambulation like PAD. Additionally, pain in lumbar stenosis radiates from the back to the leg, whereas pain in PAD radiates from the leg to the back.

Peripheral Neuropathy

Peripheral neuropathy is damage or disease affecting nerves that can impair sensation, movement, gland, and organ function. Diabetic neuropathy, one of the most common peripheral neuropathies, typically presents with a stocking-glove distribution that results may result in numbness, burning, tingling, impaired fine coordination, and difficulties with balance. The reliability of reporting these symptoms, however, is inconsistent, so clinicians should maintain a high degree of suspicion if the patient is diabetic. Diabetes is a strong risk factor for PAD and many diabetics often have coexisting PAD. The presenting history of gradually worsening peripheral sensation not relieved by rest may indicate diabetic neuropathy. Furthermore, diabetic neuropathy presents bilaterally, and PAD may present unilaterally depending on where the occlusion is. ABIs should be performed in any diabetic suspected of having PAD for further confirmation.

Peripheral Nerve Pain from a Herniated Disk Affecting the Sciatic Nerve

When a herniated disk affects the sciatic nerve, it may present with muscular weakness and pulsating radicular pain that comes and goes. Unlike PAD, the pain will often follow the distribution of the sciatic nerve and is affected by position. The history may also suggest an inciting event, such as a back injury, that would suggest herniation rather than PAD. Straight-leg may also be useful in differentiating the etiology.

Osteoarthritis of the Knee

The patellofemoral joint and medial tibiofemoral joint are most commonly associated with osteoarthritis of the knee. Pain is usually isolated to the anterior knee, but in severe disease may radiate distally. Posterior knee pain is rare unless there is a concurrent Baker's cyst. Pain is usually made worse by climbing up or going down stairs or inclines and rising from a seated position, whereas in PAD these symptoms are less dramatic. Physical exam may reveal bony deformities, including fixed flexion and/or varus presentation. X-rays may show osteophyte formation, joint space narrowing, subchondral sclerosis, and subchondral cyst formation, findings not commonly associated with PAD.

Venous Claudication

Chronic lower extremity venous disease refers to the presence of morphological or functional venous abnormalities that can cause lower extremity pain and discomfort. Visibly dilated veins, skin changes and ulcerations, tired and heavy legs, and limb swelling are frequently associated venous disease. If claudication symptoms occur, they typically present with variable degrees of leg swelling, varicosities, and increased discomfort with limb dependency, features that are not typically seen in PAD.

Symptomatic Baker's Cyst

A Baker's cyst is a swelling in the popliteal fossa due to enlargement of the gastrocnemius-semimembraneous bursa. Symptoms include posterior knee pain, knee stiffness, and the presence of a swelling or mass behind the knee detected on extension at the knee. Symptoms may worsen with activity but usually correlate with the size of the cyst, associated joint pathology, and the presence of complications that include dissection and rupture. Ultrasound and plain radiography can be used to confirm the diagnosis if it remains in question.

Chronic Compartment Syndrome

Chronic compartment syndrome results from increased pressure of the osteofacial planes of the muscle compartment due to overuse, typically from running. Unlike PAD, chronic compartment syndrome affects young endurance athletes, particularly those who run extensively. The pain is often bilateral in nature and localized to the lower leg, begins within minutes of running, and resolves within 10-20 minutes of activity cessation.

Restless Leg Syndrome

Restless leg syndrome is a sleep-related movement disorder characterized by uncomfortable need to move one's legs during periods of inactivity, sometimes accompanied by tingling, cramping, and itchiness. Symptoms usually occur in the evenings and unlike PAD, are transiently relieved by movement.

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