

Peripheral Artery Disease

What is Peripheral Arterial Disease (PAD)? A type of arteriosclerosis, involving deposits of fatty substances, calcium, and fibrin in the inner lining of the artery in the arms or, more usually, the legs.

INTRODUCTION

Cardiovascular disease is indisputably the current leading cause of morbidity and premature deaths of modern era medicine. Approximately 14 million people today in the United States have a history of myocardial infarction (MI), angina pectoris, or both, while the annual incidence is reported at 1.5 million cases. Many of the risk factors for coronary artery disease are applicable to patients with peripheral vascular disease (PVD), as both are manifestations of atherosclerotic disease.¹ However, the term *peripheral vascular disease* should be avoided when referring specifically to PAD since it fails to convey the nature of the problem and is more appropriately used to designate a group of diseases affecting blood vessels, including PAD, vasculitis, vasospasm, venous thrombosis, venous insufficiency, and lymphatic disorders.²

Nonetheless, up to two thirds of patients with a significant cardiovascular event make incomplete recoveries. Optimistically, patients with PVD can be assured that less than one third of patients require any surgical or radiologic intervention, with approximately 4-8% resulting in amputation; however, this fact should not minimize the statistical data that predict that patients with symptomatic PVD have at least a 30% risk of death within 5 years and approximately 50% in 10 years, secondary to MI or cerebrovascular disease.^{1,2}

EPIDEMIOLOGY

Systemic manifestation of arteriosclerosis commonly presents as peripheral arterial disease (PAD), and affects approximately 20% of the geriatric population. Peripheral arterial occlusion of the extremities often results from atherosclerotic plaques (atheromas), thrombus, or an embolism.

Interestingly, in contrast to coronary heart disease, women have the same risk of development of PAD as men. Patients with type II diabetes mellitus have a four-fold increased risk of PAD as compared with a two-fold increased risk of myocardial infarction or stroke. However, the severity of PAD is not directly correlated with glycemic control but rather with the coexistence of cardiovascular risk factors in addition to diabetes.³

Patients with PAD complain of pain, tightness of muscles, fatigue, or weakness of the legs on walking. This symptom is termed *intermittent claudication*, which means to limp intermittently.⁴ Symptoms are relieved by rest within a few minutes. The incidence of intermittent claudication in men ranges from 6 per 10,000 at 30 to 44 years of age to 61 per 10,000 at 65 to 74 years of age. In women, the incidence ranges from 3 per 10,000 at 30 to 44 years of age up to 54 per 10,000 at 65 to 74 years of age.

Less information is available regarding the incidence of critical limb ischemia. In a prospective 7-year study of hospitals in northern Italy, the incidence of critical limb ischemia was 450 per million population per year, and the incidence of amputation was 112 per million per year.⁵ The prevalence of PAD based on ankle-brachial blood pressure ratios is approximately 3% in persons younger than 60 years and increases to 20% in those older than 70 years.

Physicians commonly neglect subtle signs of PAD during the patient history and physical.⁶ When patients with PAD are assessed by history alone, the physician will recognize the presence of significant coronary disease only 20 to 40% of the time.^{3,5}

PATHOPHYSIOLOGY

The hemodynamic significance of arterial stenosis is a function of not only the percent stenosis but also flow velocity across the lesion. For example, resting blood flow velocity in the femoral artery may be as low as 20 cm/second; at this velocity a stenosis will not become hemodynamically significant until it is 90%

occlusive.³ With exercise in a normal extremity, however, flow velocity may increase to as high as 150 cm/second; at these higher flow velocities a stenosis becomes hemodynamically significant at approximately 50%. Thus patients with claudication will have normal flow to skeletal muscle at rest but markedly impaired flow to meet metabolic demand with exercise.

The hemodynamic significance of arterial occlusive disease can easily be assessed by measuring the systolic blood pressure in the ankle and forming a ratio of that pressure to the systolic blood pressure in the arm. This is defined as the ankle-brachial index (ABI).^{1,3,5,6} In a normal extremity with exercise, ankle blood pressure increases in proportion to the increase in arm blood pressure. With PAD, however, ankle blood pressure will become markedly reduced following exercise. When blood flow in the extremity is reduced at rest, symptoms of severe chronic leg ischemia will develop. In contrast to claudication, severe leg ischemia affects the most distal portion of the extremity with ischemia to the skin and subcutaneous tissues of the forefoot. These patients have ischemic rest pain, distal ulceration, and gangrene.³

RISK FACTORS

Atherosclerosis accounts for the overwhelming majority of causative lesions. The well-known modifiable risk factors associated with coronary atherosclerosis also contribute to atherosclerosis of the peripheral circulation. (**Table-1**) The most important independent risk factors for atherosclerosis are hypercholesterolemia, hypertension, cigarette smoking, and diabetes mellitus.⁷

Hypercholesterolemia (i.e., total serum cholesterol greater than 200 mg/dl) is clearly associated with increased risk of PAD. Of great prognostic significance is the relative apportioning between the subclasses of cholesterol-carrying lipoproteins--the low density fraction (LDL), which is atherogenic, and the high-density fraction (HDL), which exerts an atheroprotective effect by "reverse transport" of cholesterol. In a large Israeli study involving 10,059 men aged 40 to 65 years, the odds ratio for development of claudication was 1.35 for each increase in serum cholesterol of 50 mg/dl.⁸ Similar observations were made in the Framingham Heart Study, in which the odds ratio for claudication was 1.2 for each 40-mg/dl increase in total cholesterol.⁹

Other contributing factors for PAD development include genetic predisposition and diet. Genetic variability in cholesterol metabolism provides a mechanism for the well-known familial clustering of premature atherosclerotic disease. An important role for diet is strongly suggested by the variation in prevalence noted among different nations and ethnic groups, with a clear increase associated with consumption of the so-called Western diet (i.e., high fat, low fiber). The potential effects of numerous dietary components, both protective and atherogenic, have been intensely investigated with only limited consensus.⁷

TABLE -1 Risk of peripheral arterial disease in persons with modifiable risk factors

RISK FACTOR	ESTIMATED RELATIVE RISK
Cigarette smoking	2.0–5.0
Diabetes mellitus	3.0–4.0
Hypertension	1.1–2.2
Hypercholesterolemia (per 40- to 50-mg/dl increase in total cholesterol)	1.2–1.4
C-reactive protein	2.1
Fibrinogen (per 0.7-gm/liter increase in fibrinogen)	1.35
Hyperhomocysteinemia	2.0–3.2

Cigarette smoking is associated with a three- to four-fold increase risk for PAD and is synergistic with other risk factors; the prevalence of cigarette smoking in the PAD population is approximately twice that of the general population.³ In the Whitehall Study, approximately 84 percent of patients with claudication were current smokers or ex-smokers¹⁰, and in another large recent study, 90 percent of patients with PAD were current or former smokers.¹¹ Cigarette smoking is strongly associated with the incidence of atherosclerosis as well as with increased morbidity and mortality rates from its coronary, cerebral, and peripheral manifestations. The mechanism for the effects of smoking is likely to involve direct toxicity of tobacco metabolites on the vascular endothelium, probably by creating oxidant stress.⁷

In patients with diabetes mellitus, PAD is often extensive and severe, and these patients have a greater propensity for vascular calcification. Involvement of the femoral and popliteal arteries is similar to that of nondiabetic persons, but distal disease affecting the tibial and peroneal arteries occurs more frequently. The risk of development of PAD increases threefold to fourfold in patients with diabetes mellitus.²

Additional causes of PAD, although far less common than atherosclerosis, must also be considered, especially in patients who do not fit the risk factor profile outlined above. These include thromboangiitis obliterans (Buerger's disease), Takayasu's arteritis, giant cell/temporal arteritis, and other less common vasculitides. Each of these disorders has unique clinical, radiographic, and anatomic features.⁷

Hypertension alone increased the risk of claudication 2.5-fold in men and 4-fold in women in the Framingham Heart Study, and the risk increased proportionally with the severity of hypertension.⁹ An increase in fibrinogen is also associated with an increased risk of PAD.⁷

Further links to PAD as well as coronary heart disease have been established with elevated homocysteine levels. Hyperhomocysteinemia increases the risk of atherosclerosis by approximately twofold to threefold. High levels of homocysteine have been detected in 30 to 40 percent of patients with PAD.¹²

Moreover, patients with PAD have elevated levels of C-reactive protein, a serological marker of systemic inflammation. In the Physicians' Health Study, the relative risk of development of PAD among men in the highest quartile for C-reactive protein concentration was 2.1.¹³

CLINICAL FEATURES

The two cardinal symptoms of PAD are intermittent claudication and pain at rest.^{1,2,4,5,7} Claudication occurs when skeletal muscle oxygen demand during effort exceeds the blood supply and results from activation of local sensory receptors by the accumulation of lactate or other metabolites (**Figure-1**).

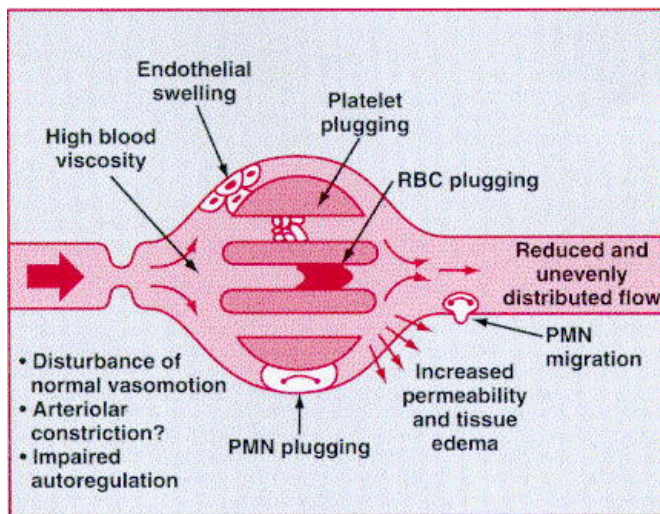


Figure-1. Schematic representation of potential pathophysiological mechanisms that lead to microvascular obstruction in patients with critical limb ischemia. (From Second European Consensus Document on chronic critical leg ischemia. *Circulation* 84[Suppl 4]:1-26, 1991.)

The location of the symptom often relates to the site of the most proximal stenosis. Buttock, hip, or thigh claudication is typical of patients with obstruction of the aorta and iliac arteries. Calf claudication occurs in patients with femoral and popliteal artery stenosis. The gastrocnemius muscle consumes more oxygen during ambulation than do other muscle groups in the leg and therefore causes the most frequent symptom reported by patients. Ankle or pedal claudication occurs in patients with tibial and peroneal artery disease. Similarly, stenosis of the subclavian, axillary, and brachial arteries may cause shoulder, biceps, or forearm claudication, respectively.²

Claudication may occur in one leg only (40% of the time) or affect both legs (60% of the time). Physicians should ascertain the severity by the distance that the patient can walk before experiencing discomfort (initial claudication distance) and before being forced to stop (absolute or maximal claudication distance). Any recent change should be determined.³

Although most patients with only intermittent claudication have normal appearing limbs, generally, the classic presentation of patients with acute ischemia of the extremities may be recalled by the "five Ps": *pain*, *palor*, *pulselessness*, *paresthesias*, and *paralysis*.⁷

The degree of pain depends on the severity of ischemia, which is generally determined by the location of the occlusion and the degree of collateral flow. Pallor is a common but relative finding that depends on the degree of ischemia and the underlying skin color. A sudden and complete embolic occlusion may result in a

cool, waxy appearing white extremity with no signs of cutaneous blood flow. Normally, pulses that are readily palpable in healthy individuals include the brachial, radial, and ulnar arteries of the upper extremity and the femoral, popliteal, dorsalis pedis, and posterior tibial arteries of the lower extremities. The aorta also can be palpated in asthenic persons.³ The absence of arterial pulses on examination should alert the physician to both the location of the arterial occlusion and the degree of ischemia. Patients with acute arterial embolism generally have normal palpable pulses above the occlusion with a complete absence below.⁴ A list of physical signs that may point to PAD can be found in **Table-2**.^{1-4,6,7}

Within the extremities, peripheral nerve is the tissue that is most sensitive to ischemia. As such, the degree of neurologic dysfunction is a sensitive indicator of the degree of ischemia. With mild ischemia, the findings may be subjective and subtle. Early paresthesias may be characterized as a numbness of the toes or a slight decrease of sensation of the foot compared with the contralateral extremity. With severe ischemia, however, profound sensory loss may lead to complete anesthesia of the foot, indicative of impending tissue loss without early revascularization efforts.

TABLE-2 Physical signs of PAD --Limb examination and comparison to opposite limb includes:

<ul style="list-style-type: none"> • Hair Loss • Poor nail growth • Dry, Scaly, atrophic skin • Arterial Bruits • Persistent cyanosis 	<ul style="list-style-type: none"> • Pallor with leg elevation after one minute at 60 degrees (normal color should return in 10-15-sec.; longer than 40 seconds indicates severe ischemia) • Ischemic, gangrenous tissue • Absent or diminished femoral or pedal pulses • Dependent rubor
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Tightness and discomfort in the calf, precipitated by exercise, may sometimes result from a chronic compartment compression syndrome; such patients are often athletes with large calf muscles. Calf claudication may also develop in athletes from popliteal entrapment caused by external muscle compression of the popliteal artery.^{4,5}

In contrast, several nonvascular causes of exertional leg pain should be considered in patients with symptoms suggestive of intermittent claudication (**Table-3**). Pain from arthritis of the hip or knee is often present at rest and exacerbated by exercise. With cessation of exercise, the pain may not improve unless the patient rests and unloads the joint. Claudication-like symptoms may also arise from spinal stenosis, which is due to osteophytic narrowing of the lumbar neurospinal canal.³ McArdle syndrome, characterized by a deficiency of skeletal muscle phosphorylase, can cause symptoms mimicking the claudication of PAD. Patients with chronic venous regurgitation may complain of leg discomfort with exertion, a condition designated venous claudication.^{2,3}

Differential Diagnosis (see Appendix-1)

TABLE- 3 –Differential diagnosis of intermittent leg claudication

Vascular Causes	Nonvascular Causes
Atherosclerosis	Lumbosacral radiculopathy
Thrombosis; Deep vein thrombosis	Degenerative arthritis
Embolism	Spinal stenosis
Vasculitis	Herniated disc
Thromboangiitis obliterans	Arthritis of Hip, knees
Takayasu arteritis	Venous insufficiency
Giant cell arteritis	Myositis
Aortic coarctation	McArdle syndrome
Fibromuscular dysplasia	
Irradiation	
Extravascular compression	
Arterial entrapment (e.g., popliteal artery entrapment, thoracic outlet syndrome)	

TABLE- 4 Fontaine classification of PAD

STAGE	SYMPTOMS
I	Asymptomatic
II	Intermittent claudication
IIa	Pain free, claudication walking >200 meters
IIb	Pain free, claudication walking <200 meters
III	Rest and nocturnal pain
IV	Necrosis, gangrene

Categorization of PAD

Patients with PAD may be classified according to the severity of the symptoms and abnormalities detected on physical examination. The traditional scheme described by Fontaine classified patients in one of four stages progressing from asymptomatic to critical limb ischemia (**Table 4**). A contemporary, more descriptive classification has been adopted by several professional vascular societies and includes asymptomatic patients, three grades of claudication, and three grades of critical limb ischemia ranging from rest pain alone to minor and major tissue loss (**Table 5**).^{2,14}

TABLE -5 Clinical categories of Chronic Leg Ischemia

GRADE	CATEGORY	CLINICAL DESCRIPTION
0		Asymptomatic, not hemodynamically correct
1	I	Mild claudication
2		Moderate claudication
3		Severe claudication
4	II	Ischemic rest pain
5		Minor tissue loss: nonhealing ulcer, focal gangrene with diffuse pedal ulcer
6	III	Major tissue loss extending above the transmetatarsal level, functional foot no longer salvageable

Adapted from Rutherford RB, Baker JD, Ernst C, et al: Recommended standards for reports dealing with lower extremity ischemia:

Revised version. J Vasc Surg 26:517–538, 1997.

DIAGNOSTIC PROCEEDURES

Although the diagnosis of peripheral arterial disease can be made clinically, noninvasive and invasive tests can help confirm and delineate the extent of the disease process. Noninvasive tests frequently used to diagnose arterial insufficiency include ankle/brachial index (ABI), ultrasound, treadmill exercise testing, and magnetic resonance angiography (MRA).^{1,4}

Segmental Pressure Measurement

Measurement of systolic blood pressure in the ankle by Doppler ultrasound has become *the standard* for the initial evaluation of all patients with vascular disease.^{1,2,6} Specifically, in the lower extremities, measurement of pressure plays a central role in the assessment of disease severity. Segmental pressure measurements in the limb are used to localize and grade hemodynamically significant lesions, as well as the overall degree of circulatory impairment.

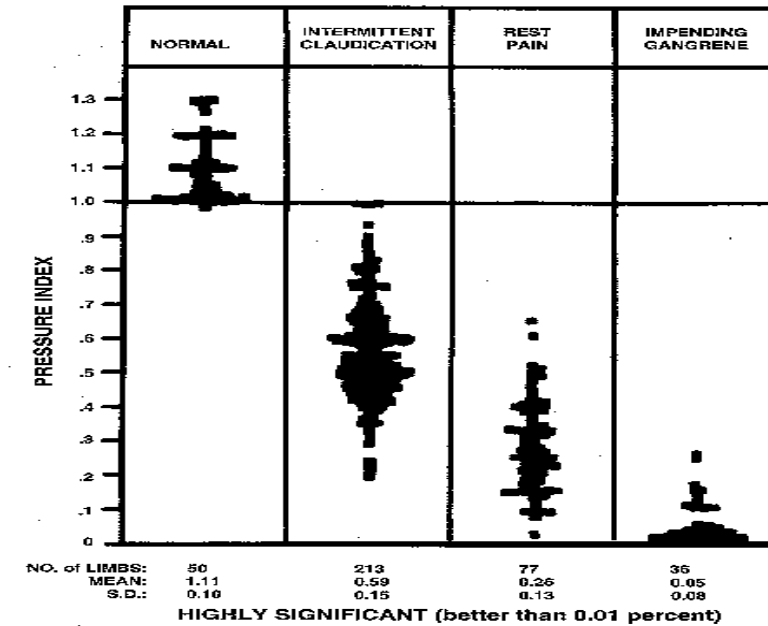
The single most useful index is the ankle pressure, which can be obtained simply at the bedside with a handheld Doppler probe and pressure cuff. The cuff is placed around the lower calf just above the malleolus and the Doppler probe is positioned over the dorsalis pedis or posterior tibial arteries to obtain a flow signal. The cuff is inflated and then slowly deflated, and the examiner records the pressure at which the audible signal returns. Likewise, in the upper extremity, pneumatic cuffs are placed on the upper part of the arm over the biceps, on the forearm below the elbow, and at the wrist.^{4,6,7}

Taking into consideration the precision of this noninvasive method and the variability in blood pressure over short periods, a blood pressure gradient in excess of 20 mm Hg between successive cuffs is generally used

as evidence of arterial stenosis in the lower extremity, whereas a 10 mm Hg gradient between sequential cuffs in the upper extremity is indicative of stenosis.² The ankle systolic blood pressure at rest normally is more than 90% of the brachial pressure, with mild arterial insufficiency between 70% and 90%, moderate insufficiency between 50% and 70%, and severe insufficiency below 50%. (1)

Ankle/Brachial Index

Because the ankle pressure varies with central aortic pressure, it is commonly indexed to the brachial artery pressure as a ratio (ankle-brachial index, or ABI). *The ABI is the ratio of systolic blood pressure measured at the ankle to systolic blood pressure at the brachial artery.* In normal



resting subjects, the ABI is slightly greater than unity (1.0 to 1.2). There is a correlation between the severity of signs and symptoms of arterial insufficiency and the ABI (Figure-2), such that claudicants usually fall in the 0.5 to 0.7 range, whereas critical ischemia (rest pain or tissue necrosis) most commonly is associated with an ABI less than 0.4. The most common source of error in the ABI is false elevation resulting from extensive vascular calcification, as is common in diabetic patients or those with chronic renal failure.^{2,7}

Figure-2: Correlation between signs and symptoms of lower extremity arterial insufficiency and the ankle/brachial index. (From Yao JST: Hemodynamic studies in peripheral arterial disease. Br J Surg 57:761, 1970.)

Doppler and Duplex Ultrasonography

Continuous-wave and pulsed-wave Doppler systems transmit and receive high-frequency ultrasound signals. The Doppler frequency shift caused by moving red blood cells is proportional to the velocity of blood flow. The Doppler probe is positioned at approximately a 60-degree angle over the common femoral, superficial femoral, popliteal, dorsalis pedis, and posterior tibial arteries. A normal Doppler waveform has three components: a rapid forward flow component during systole, transient flow reversal during early diastole, and a slow antegrade component during late diastole. The Doppler waveform becomes altered if the probe is placed distal to an arterial stenosis and is characterized by deceleration of systolic flow, loss of the early diastolic reversal, and diminished peak frequencies.^{1,2}

Duplex ultrasound plays a central role in several areas of vascular practice. The most common application is for carotid bifurcation disease. Duplex scanning allows for precise anatomic localization of lesions, quantitates their severity, and, with the development of higher resolution systems, can even assess plaque morphology! (Figure-3) Lower extremity Duplex arterial mapping has been touted as an imaging strategy to determine patient suitability for angioplasty or bypass.

Color-assisted duplex ultrasound imaging is an effective means of localizing peripheral arterial stenosis. Normal arteries have laminar flow with the highest velocity at the center of the artery. The representative color image is usually homogeneous, with relatively constant hue and intensity. In the presence of an arterial stenosis, blood flow velocity increases through the narrowed lumen. As the velocity increases, progressive desaturation of the color display can be noted, and flow disturbance distal to the stenosis causes changes in hue and color. A twofold or greater increase in peak systolic velocity at the site of an atherosclerotic plaque indicates a 50 percent or greater diameter stenosis. A threefold increase in velocity is suggestive of a 75 percent or greater stenosis. No Doppler signal is obtained if the artery is occluded.^{2,15}

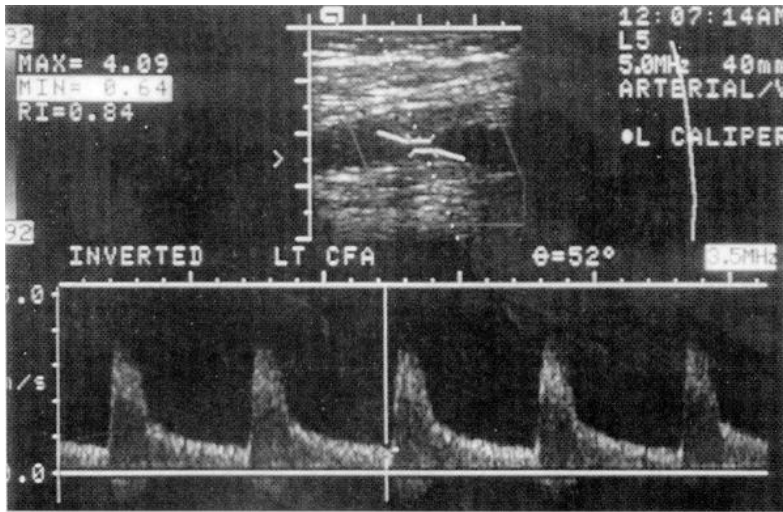


Figure-3. Duplex ultrasound of the common femoral artery. The *upper* image shows a gray-scale image of the artery in which plaque is present and encroaching on the lumen. The *lower* image is a recording of the pulsed Doppler velocity sampled from the common femoral artery. The peak velocity of 350 cm/sec is elevated. These features are consistent with significant stenosis.

Treadmill Exercise Testing

Treadmill exercise testing is used to evaluate the clinical significance of peripheral arterial stenosis, and to provide objective evidence of the patient's walking capacity. Treadmill testing provides a means to determine whether arterial stenosis contribute to the patient's symptoms of exertional leg pain. Normally, the blood pressure increase that occurs during exercise should be the same in both the upper and lower extremities, with maintenance of constant ABI of 1.0 or greater. In the presence of peripheral arterial stenosis, the ABI decreases because the increase in blood pressure that is observed in the arm is not matched by a comparable increase in ankle blood pressure.

When compared with healthy individuals of the same age, patients with claudication have a 50 to 60% reduction in peak treadmill performance, a severity similar to that of patients with severe congestive heart failure. Patients are typically tested at a slow speed not to exceed 2 miles/hour, with the treadmill grade beginning at 0% and increasing 2% every 2 minutes until maximal symptoms prevent further exercise. The initial claudication distance is defined as the point at which symptoms of claudication first develop, and the absolute claudication distance is the point at which the patient is no longer able to continue walking because of severe leg discomfort.^{2,3,7}

Magnetic Resonance Angiography

MRA is a noninvasive means to visualize the aorta and the peripheral arteries.² It offers the distinct advantages of being noninvasive and avoiding contrast exposure. The most common technique used for obtaining vascular enhancement is time-of-flight (TOF), in which brightness is directly related to the velocity of blood entering the slice. As a result, lesion severity is often overestimated, which is an important limitation.⁷ Comparative studies have reported sensitivities of 93 to 100 percent and specificities of 96 to 100 percent for the aorta, iliac, femoral-popliteal, and tibial-peroneal arteries.¹⁶ MRA is particularly useful in patients who are at high risk for contrast-induced nephropathy, particularly elderly diabetics.²

MEDICAL TREATMENT

Medical therapy in patients with PAD should be designed to reduce cardiovascular morbidity and mortality by treating systemic atherosclerosis and to improve functional status and limb preservation by

relieving claudication and severe leg ischemia. As noted earlier, cigarette smoking, diabetes mellitus, hypertension, hyperlipidemia, age >40 years, and hyperhomocystinemia increase the risk of PAD development.^{1,6} **Smoking is the most important risk factor and is correlated more closely with PAD than any other risk factor.**⁶ Therefore, smoking cessation is critical to delay the progression of PAD and reduce cardiovascular morbidity and mortality.

Medications such as vasodilators are prescribed for intermittent claudication with the general aim to increase peripheral delivery of oxygen, but its efficacy remains questionable, however most vascular specialists consider vasodilator drugs not to be of value.¹ Beta-blockers can result in peripheral vasoconstriction and are avoided in patients with arterial occlusive disease. **Pentoxifylline** (Trental) may be variably effective in patients with intermittent claudication by increasing red cell deformability, decreasing plasma viscosity, and diminishing fibrinogen concentration. The recommended dosage is 400 mg three times a day with nausea and dyspepsia as side effects. Three meta-analyses have been done; two found pentoxifylline of questionable value, while the other reported it of benefit.⁴ **Cilostazol** is a phosphodiesterase inhibitor that suppresses platelet aggregation and dilates arteries. It has been shown to significantly increase walking distance in patients with claudication at doses of 50 to 100 mg. Patients must be observed carefully for tachycardia; other frequent side effects are headache, diarrhea, dizziness, and nausea.⁴ In addition, **aspirin** in patients with PAD reduces the risk of cardiovascular mortality by approximately 25% and is considered the antiplatelet drug of choice. An aspirin dosage of 81 to 325 mg per day orally is indicated.^{3,6} **Clopidogrel (Plavix)**, an antagonist of adenosine diphosphate-induced platelet aggregation, provides a 23% relative risk reduction in the incidence of vascular death, myocardial infarction, and stroke when compared with aspirin in patients with PAD. Plavix is administered at 75mg per day orally.³

Skin Therapy

Routine prophylactic skin and foot care is extremely important in preventing skin compromise, especially in diabetic patients. Patients should inspect their feet daily for cracks, fissures, calluses, corns, and ulcers and seek early intervention from podiatrists. In diabetic patients with neuropathic ulcers, weight bearing should be avoided in the acute healing process, and then, when appropriate, orthotics should be used to redistribute pressure points and ensure proper fit of shoes. Aggressive wound care and tight management of capillary blood glucose in patients with DM further augments wound healing.¹

Exercise Therapy

A formal exercise program is the most effective treatment of PAD.^{2,6} A meta-analysis of 21 controlled studies of exercise rehabilitation found that a supervised exercise program increased the average distance walked to the onset of claudication by 179 percent and the maximal distance walked by 122 percent.¹⁷ The greatest benefit occurred when sessions were at least 30 minutes in duration at least three times per week for 6 months and when walking was used as the mode of exercise. The mechanisms through which exercise training improves claudication are not known. Studies in experimental models of hindlimb ischemia have suggested that regular exercise increases the development of collateral blood vessels.^{2,18}

INVASIVE THERAPIES

Invasive therapies should be limited to patients who fail initial medical treatment, have severe disability as defined by validated questionnaires or treadmill testing, and have an appropriate anatomic lesion for bypass or angioplasty (**Figure-4**).

Percutaneous endovascular therapy

Percutaneous techniques for treating arterial occlusions, including balloon dilatation angioplasty, stenting, thrombolytic therapy, and arterectomy have undergone tremendous development in the past quarter century. Indications include resting pain, gangrene, or progressive limiting intermittent claudication that prevents the patient from functioning. Various endpoints have served to indicate the efficacy of these interventions, including the ABI, vessel patency by duplex ultrasound or conventional angiography, relief of symptoms, and limb salvage.^{2,3}

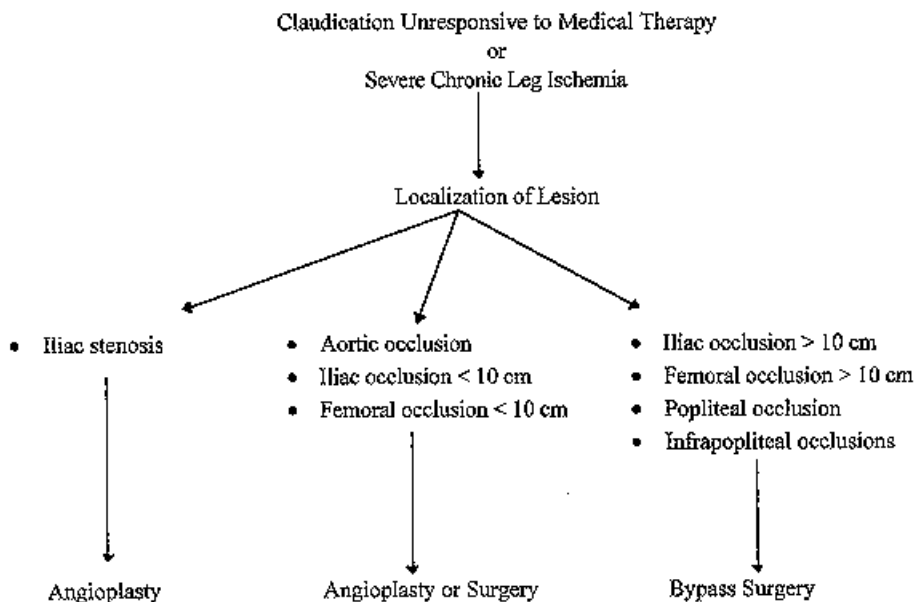


Figure-4 Interventional therapy for peripheral arterial disease.

Percutaneous Transluminal Angioplasty (PTA) carries with it a high recurrence rate of obstruction, but it is a useful treatment of localized short, segmental, and occlusive arterial lesions.^{1,18} The mechanism of dilation in balloon angioplasty is thought to involve fracture and displacement of plaque, and overstretch of the media and perhaps the adventitia as well. Specific guide wires, catheters, and balloons have

been designed for different anatomic sites. The initial technical feat is to accomplish crossing of the lesion with a guide wire, followed by appropriate positioning of the balloon catheter. In thrombolytic therapy, fibrinolytic drugs are used to enhance conversion of plasminogen to plasmin, which is then capable of degrading fibrin clot. The two major drugs in current use are urokinase and tissue plasminogen activator (tPA). The last technique is catheter-directed atherectomy. This involves the use of specially designed catheter devices to remove atherosclerotic plaque from the arterial wall by shaving, cutting, or high-speed rotational ablation.^{1,7,18}

In general, the efficacy of percutaneous interventions is better for treatment of stenosis than occlusions and when targeting vessels with good runoff (i.e., patent distal vessels) as opposed to poor runoff.⁷ Five-year patency rates range from 60-90%, depending on the vascular vessel intervened. In contrast, stents are inserted into the vessel (best in large arteries with high flow) at the site of the obstruction, and the recurrence rate reportedly is less than in PTA. However, stents do not work as well in smaller vessels and longer occlusions.

Angioplasty guidelines emphasize that more proximal lesions have better patency rates and durability than do more distal lesions. Below the inguinal ligament, the initial success and long-term patency rates are not as good as more proximal lesions. Thrombolytic therapy is most effective for acute arterial occlusions of less than 2 weeks and indicated in severely ischemic limbs.¹ For arterectomy, long-term results in the lower extremity vessels have been poor and there does not appear to be an advantage over PTA alone, which is less expensive and has fewer complications.⁷ Complications, such as thrombosis or hematomas, occur in approximately 4 to 6 percent of endovascular interventions and usually relate to the severity of arterial disease and the complexity of the procedure.^{2,7,18}

Peripheral Arterial Surgery

Surgical intervention is indicated in patients with incapacitating claudication, resting pain, gangrene, and tissue loss. Surgery is an option more likely to be pursued in patients with diffuse disease, extended occlusions, and severe arterial calcifications. Surgical procedures include bypass graft and resection with graft placement and thromboendarterectomy. The surgical procedure is planned after angiographic identification of the arterial obstruction to ensure sufficient arterial inflow to and outflow from the graft to maintain patency. Preoperative evaluation to assess the risk of vascular surgery should be performed since many of these patients have coexisting coronary artery disease.^{7,18}

At present, patients who need vascular surgery (e.g., to prevent limb loss) but are believed to be high risk on clinical grounds should have aggressive intraoperative monitoring of central and peripheral hemodynamics and modulation of their sympathetic responses during anesthesia. Only patients with extensive, symptomatic coronary artery disease in whom the coronary disease is more severe or life-threatening than the PAD should undergo additional evaluation for cardiac revascularization.^{1,7,18}

PROGNOSIS/OUTCOME

The prognosis of patients with PAD is affected by an increased risk for adverse cardiovascular events, as well as the risk of limb loss (**Figure-5**). Patients with PAD frequently have concomitant coronary artery disease and cerebrovascular disease.^{2,11} Approximately 15 to 25 percent of patients with PAD have significant carotid artery stenosis by duplex ultrasound.² Epidemiological studies have found that the risk of death from cardiovascular causes is increased 2.5- to 6-fold in patients with PAD and the annual mortality rate is 4.3 to 4.9 percent.^{2,10,11}

Worsening symptoms develop in approximately 25 percent of patients with claudication.² Clinical progression to critical limb ischemia occurs in 7.5 to 8.0 percent of patients with claudication in the first year after diagnosis and approximately 2.2 percent each year thereafter. Of patients with PAD, those with diabetes mellitus have a 21 percent risk of major amputation as compared with 3 percent in non-diabetic persons.^{2,19}

As physicians, we must help patients learn to adapt and become self-reliant and ensure they realize that they can influence their hypertension, DM, weight, and smoking activity through behavioral and lifestyle modifications. In fact, evidence has demonstrated that a doctor's advice to quit smoking increases cessation by 30%.⁶ Through the comprehensive approach of proper treatment and rehabilitation, the patient's quality of life will improve, rapidity of return to work increases, and hospital readmission reduces. However, these positive results may not occur unless the patient themselves desires to comply with the aforementioned prevention and treatment strategies.



Figure- 5 Diagram of the natural history of patients with peripheral arterial disease emphasizing both the potential outcome of the affected limb and the cardiovascular prognosis.^{2,20}

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Appendix-1 -- Differential Diagnosis of Leg Pain with Exercise

Diagnosis	Sex	Age	Frequency	Cause	Pulses
Arteriosclerosis obliterans	M>F	Seventh decade	Very common	Occluded or stenosed large or medium-sized arteries; lower extremity involvement	Abnormal
Neurogenic	M=F	Sixth-seventh decade	Common	Spinal cord compression or ischemia	Normal
Thromboangiitis obliterans	M>>F	Third-fourth decade	Rare	Vasculitis of medium to small arteries; upper and lower extremity involvement	Abnormal; loss of ulnar pulse
Adventitial cysts	M>F	Fourth decade	Rare	Unknown	Usually normal
Popliteal artery entrapment syndrome	M>F	Third-fourth decade	Rare	Abnormal origin of muscles	Usually normal
Venous claudication	M=F	Any age	Rare	Iliofemoral thrombophlebitis	Normal
McArdle's disease	M=F	Any age	Rare	Deficient muscle phosphorylases	Normal
Shin splints	M=F	Any age	Common	Swollen anterior tibial muscle	Normal

Peripheral Artery Disease

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February 2004