How to Approach a Patient with Peripheral Arterial Disease
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Abstract
Peripheral Arterial Disease (PAD) is defined as chronic atherosclerotic disease of the lower limbs. Patients with lower extremity PAD present with wide spectrum of symptoms ranging from asymptomatic to minor exertional leg pain, significant walking impairment and ulceration or gangrene. The first step in decision making for the treatment of PAD is to confirm PAD with history, physical examination and non invasive vascular laboratory tests. Decision making regarding revascularization is based on symptom status and patient comorbidities. Treatment strategies for intermittent claudication is medical management and for critical limb ischemia is revascularization in the form of either endovascular or surgical management to avoid amputation.

Keywords: Claudicant, critical limb ischemia, peripheral arterial disease

Introduction
Peripheral arterial disease (PAD) is a manifestation of systemic atherosclerosis and is associated with increased cardiovascular morbidity and mortality. Much of this is due to the effects of atheroma on the arteries supplying the heart muscle (coronary thrombosis and myocardial infarction), extremity (peripheral arterial occlusive diseases) and brain (stroke). The approach to PAD is to recognize the presence of lower extremity ischemia, quantify the extent of local and systemic disease, determine the degree of functional impairment related to PAD, identify and control modifiable risk factors, and establish a comprehensive treatment program.

Symptomatology
Patients with PAD may be asymptomatic, as many of the patients overcome their debility by walking less and walking at a slower pace. McDermott et al. compared 72 asymptomatic patients with PAD to those with claudication (n = 215) and 292 with no PAD. They found that asymptomatic patients with PAD had worse functional performance, worse quality of life, and more adverse calf muscle characteristics compared with persons with intermittent claudication (IC), as well as with the sedentary, asymptomatic, age-matched group of non-PAD persons. This underscores the impact of PAD even in asymptomatic patients who limit their activity to control symptoms or because of other medical illness.

The symptoms of PAD may be IC, rest pain, or tissue loss. Claudication is defined as a cramping type of pain involving a group of muscle, produced after walking for a particular distance, promptly relieved with rest and reproduced after walking for the same distance.

The site of pain depends on the site of arterial occlusion. The occlusion is usually one joint above the muscles affected. The most common site is the calf muscles. Thus, pain in the foot is due to occlusion in the lower tibial and plantar vessels, pain in the calf is due to occlusion in femoropopliteal segment, pain in the thigh due to occlusion in the common femoral artery, pain in the buttock is due to occlusion in the common iliac or aortoiliac segment, the aorto iliac involvement often associated with impotence is called Leriche’s syndrome.

Pain commonly develops when the muscles are exercising. The cause for pain is accumulation of substance P and other metabolites. Patients with claudication often have a single level of occlusion. Most of the times, it is difficult to differentiate from other pathologies, which mimic vascular claudication. Commonly, neurogenic pain is mistaken for vascular claudication and vice versa.

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**Differential Diagnosis**

In neurogenic claudication, pain develops while standing or walking and disappears immediately after stopping walking; pulses are normal to feel and there are no ischemic changes present in the leg. It is usually due to a narrow lumbar canal (spinal canal stenosis) and pain can be reproduced by asking the patient to touch his/her toes.

Patients with chronic venous insufficiency may also develop claudication pain, but the pain is a severe bursting pain, after walking for a long distance, and is relieved gradually on elevation of the leg. Patients also will have clinical evidence of chronic venous insufficiency with normal peripheral pulses [Table 1].

The other presentation is critical limb ischemia (CLI) which occurs in 1% of patients with PAD. CLI is defined as rest pain for >2 weeks not relieved with analgesics including opioids or tissue loss; Ankle Brachial Pressure Index (ABI) <0.4; ankle pressure <50 mmHg; toe pressure <30 mmHg. In diabetic patients, mere absence of pulse defines CLI.

The common major manifestations of CLI are rest pain and ischemic ulceration or gangrene of the forefoot and toes representing a reduction in distal perfusion below resting metabolic requirements. Rest pain is usually described as a burning sensation or as an uncomfortable coldness or paraesthesia of sufficient intensity to interfere with sleep. Factors responsible for pain at night are low cardiac output, loss of gravitational pull, and cutaneous vasodilatation.

The discomfort is worsened by leg elevation because of the loss of gravitational pull of blood to the foot; it is relieved by placing the limb in a dependent position, such as dangling it off the side of the bed.

CLI patients usually have multiple level of arterial occlusion in contrast to claudicants who usually have single level of occlusion. This multilevel occlusion may be either sequential like iliac artery occlusion combined with femora popliteal occlusion or parallel such as occlusion of superficial femoral artery, profound femurs artery, thereby effectively blocking the opportunity for collateral formation.

CLI is associated with a higher risk of limb loss in the absence of revascularization, whereas, claudication rarely progresses to the point of requiring amputation.

**Etiology**

- Atherosclerosis (most common)
- Thromboangitis obliterans
- Vasculitis
- Takayasu arteritis
- Giant cell arteritis
- Atheroembolism
- Peripheral embolism from
- Proximal vessel thrombus
- Aneurysm
- Cardiac source
- Popliteal entrapment syndrome
- Thrombosis in situ
- Fibromuscular dysplasia
- Radiation arteritis
- Trauma
- Extrinsic compression.

**Risk Factors**

The common modifiable risk factors for occlusive arterial

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**Table 1: Differential diagnosis**

| Condition           | Etiology                                                      | Character of pain                   | Location        | Presentation                                         |
|---------------------|---------------------------------------------------------------|------------------------------------|-----------------|------------------------------------------------------|
| Calf IC             | Occlusion of femora popliteal segment                         | Burning, cramping, aching          | calf muscles    | Occurs with walking, exercise relieved by rest        |
| Thigh and buttoc IC | Occlusion of ileo femoral segment                             | Burning, cramping, aching          | Buttocks, hip, thigh | Occurs with walking, exercise relieved by rest        |
| Foot IC             | Occlusion of tibial segment                                   | Severe pain on exercise            | Foot arch       | Occurs with walking, exercise relieved by rest        |
| Venous claudication | Deep vein thrombosis, chronic venous insufficiency            | Tight, bursting pain               | Entire leg, worse in calf | Occurs with walking, relieved by elevating the leg    |
| Chronic compartment syndromes | Arterial insufficiency resulting from venous congestion and compartment tissue hypertension | Tight, bursting pain | Anterolateral aspect of leg | Occurs with vigorous exercise (jogging), relieved by rest |
| Neurogenic claudication | Lumbosacral neurospinal nerve root compression | Diffuse, deep aching or burning may be associated with distal parasthesias and numbness | Extends from buttocks to feet | Occurs with sitting, standing walking; relieved by change in position |
| Symptomatic Baker cyst |                                                  | Swelling and tenderness            | Behind knee, down calf | Occurs with exercise, present at rest                 |
| Hip arthritis       | Aching, discomfort                                           |                                    | Lateral hip and thigh | Occurs with exercise, Improved when not weight bearing |
| Foot/ankle arthritis | Aching pain                                                  |                                    | Ankle, foot arch | After variable degree of exercise. May be relieved by not bearing weight |

IC: Intermittent claudication
disease are smoking, hypertension, diabetes mellitus, and dyslipidemia.

Risk factors for atherosclerosis
- Advanced age
- Male gender
- Smoking
- Diabetes mellitus
- Dyslipidemia
- Hypertension
- Hyperfibrinogenemia
- Hyperhomocysteinemia
- Hyper coagulability
- Elevated C-reactive protein
- Chronic renal insufficiency.

Diagnosis

History and physical examination
A complete history and physical examination of patients with PAD is important, and focus on the legs, as well as systemic risk factors is essential. Vasculogenic and neurogenic claudication must be differentiated, as also other causes for leg ulcers and other nonvascular etiologies for leg symptoms.

Signs of CLI are as follows:
- Marked pallor, purple blue cyanosed appearance
- Thinning of skin
- Diminished hair
- Loss of subcutaneous fat
- Brittle nails, with transverse ridges
- Ulceration in digits
- Wasting of muscles
- Temperature (cold).

Ankle Brachial Index (ABI) [Table 2] is calculated as follows:

Ankle Brachial Index = \frac{\text{Higher ankle pressure}}{\text{Higher arm pressure}}

Toe Brachial Index
Digital toe pressure is more useful when ankle pressure is not reliable because of calcified tibial vessels particularly in diabetic patients, in whom the digital vessels are usually spared. Normal toe pressure is 20–40 mmHg less than the ankle pressure. Toe brachial index <0.7 is considered abnormal.

Segmental pressure measurements
Segmental pressure is measured at multiple levels (upper and lower thigh, upper calf, and ankle); pressure reductions between levels help to localize the occlusion; normally pressures increase as one moves further down the leg (>20 mmHg gradient abnormal); test is inaccurate in calcified artery walls.

Hematologic studies
At initial presentation, a patient with manifestations of PAD should undergo a battery of basic hematologic studies to characterize risk factors and identify end-organ involvement.

Blood tests to exclude anemia, diabetes, renal disease, and lipid abnormalities should include a full blood count, blood glucose, lipid profile, and serum urea and electrolytes. High blood viscosity (polycythemia and thrombocytosis) may be caused by smoking but may also be associated with cancer. Renal impairment (raised serum creatinine and low glomerular filtration rate) may be caused by drugs and may be exacerbated by intravenous contrast agents used during angiography.

Cardiac and pulmonary evaluation
An electrocardiogram (ECG) may show coronary ischemia, left ventricular hypertrophy, or rhythm abnormalities, although a normal ECG does not rule out these conditions. More information may be gained by a cardiac echo or exercise testing. Stress echo may be performed in patients with claudication as these patients find it difficult to do exercise testing. Arterial blood gases and pulmonary function test may be appropriate in patients with severe lung disease.

Duplex scan
Duplex scan is an important investigation to localize the site of lesion and to plan the management. However, the main application of Duplex scan is for postoperative graft surveillance.

Angiography
Angiography is invasive and is done only when intervention is being contemplated.

Computed tomography/magnetic resonance angiogram
Computed tomography (CT) angiography and magnetic resonance (MR) angiography are noninvasive, new techniques gaining in popularity although the image quality is not as good as digital subtraction angiography.

Three-dimensional multidetector CT has become the first-line study for PAD when planning for revascularization. Arterial wall calcification is better seen with this technique. It also helps to evaluate the adjacent structures. The main limitations are use of contrast and radiation exposure. The risk of contrast-induced nephropathy should always be anticipated.

In all patients, pre- and post-procedure hydration is mandatory to prevent contrast-induced nephropathy. The protocol followed in our institute is infusion of normal saline 100 ml/h 12 h pre- and post-procedure, unless there are contraindications such as congestive cardiac failure. As a routine N-Acetylcysteine 600 mg twice a day is started a day before angiogram and continued for 3 days.
**Carbon dioxide arteriography**
Carbon dioxide (CO₂) arteriography is used for imaging in patients with chronic kidney disease where iodinated contrast is contraindicated and in patients with contrast allergy. Injection of CO₂, with its decreased radiodensity creates radiographic contrast by transiently displacing blood from the artery being imaged.

**Treatment**
Management of PAD must be structured according to the symptomatology and the presentation [Figure 1].

**Claudicants**
All patients with PAD should have risk factor modification in an effort to limit the progression of the atherosclerotic. Therapy geared toward the relief of symptoms and the stabilization of existing atherosclerosis is also essential. This subset is at significantly increased risk for premature cardiovascular events, including myocardial infarction, stroke, and death. Detection of occult PAD is an important indirect marker for systemic atherosclerosis.[7]

Most patients with IC require nonoperative management, should quit smoking, and have regular exercise (walking) leading to improvement of symptoms. A few could be considered for intervention if they have disabling claudication that limits their daily routine or interfere with professional performance.

**Pharmacologic treatment of claudication**
Several drugs have been suggested, but only two drugs (pentoxifylline and cilostazol) have been approved by the Food and Drug Administration for the treatment of IC in the United States. Of these, cilastazol has got proven benefit.[8]

**Pentoxiphylline**
It is a methylxanthine derivative that is thought to improve oxygen delivery because of its rheolytic effect on red blood cell wall flexibility and deformability, ultimately reducing blood viscosity.

**Cilastazol**
Oral administration of this phosphodiesterase III inhibitor increases cyclic adenosine monophosphate results in a variety of physiologic effects, including inhibition of smooth muscle cell contraction and platelet aggregation. It is contraindicated in patients with congestive cardiac failure.

**Exercise therapy for claudication**
Multiple reports have clearly demonstrated improvements[9-11] in pain-free ambulation and overall walking performance with structured exercise training. Regular aerobic exercise reduces cardiovascular risk by lowering cholesterol and blood pressure and by improving glycemic control. Walking regularly within the limits of the disability is ideal and should be done for 30–45 min 4–5 times a week.

**Critical Limb Ischemia**
Patients with CLI, i.e. rest pain or ulcer/gangrene require urgent revascularization to prevent limb loss.

**Transatlantic Inter Society Consensus II Classification**
The Transatlantic Inter Society Consensus (TASC) working group advocated endovascular treatment for TASC type A lesions and open surgical treatment for TASC type D lesions. For TASC type B and C lesions, the authors concluded that there was insufficient evidence to definitively recommend one modality over the other[12] [Figure 2].

**Endovascular treatment: Transluminal angioplasty and stenting**
Arterial stenosis or occlusive disease may be treated by inserting a balloon catheter into an artery and inflating it within a narrowed or blocked area. Occasionally, if the vessel “re-coils” after angioplasty or the lesions requires repeated interventions and is not a long segment, the artery may be stented or considered for a bypass.

With improvements in the availability of wires, catheters, stents, and available expertise, endovascular options seem to be on the rise.

A word of caution from the authors is that this modality should be judiciously used as majority of the Indian population pay “out of pocket” for their treatment.

**Surgical Management**
Surgical revascularization is done depending on the level of occlusion.

Intervention can range from an endarterectomy with or without a patch; ilio-femoral, aorto-bifemoral or uni-femoral, femoro-femoral, axillo-uni or bifemoral, femoro-popliteal, femoro-distal, bypass.

The conduit preferred for bypass surgery is Dacron® or ePTFE when the supply is from the aorta, iliac or axillary artery and vein (as long as its diameter is at least 3 mm and not thick walled) for bypasses from the femoral and below.

**No Option Critical Limb Ischemia**
Some patients may not have a suitable distal vessel small caliber, not crossing the ankle joint, for revascularization, they are termed as no option CLI. Treatment options for these patients are discussed in the following sections.

**Lumbar sympathectomy**
The only indication in the present era is thrombo angitis obliterates (Buerger’s disease) with nonreconstructable vessel.

**Intermittent Pneumatic Compression**
Intermittent pneumatic compression (IPC) in combination with appropriate risk factor modification may be a viable method of treatment for patients with nonreconstructable vascular disease, for those who are physiologically unfit for surgical intervention, or for patients with IC who do not want invasive treatment. Ilayakumar et al.[13] in a pilot study of ten patients
showed that IPC helps patients with nonrevascularisable CLI as a limb salvage option, who otherwise carry a high risk of major amputation.

IPC involves sequential inflation and deflation of pneumatic pressure cuffs positioned at the foot or calf. Inflation-deflation rates vary according to the system used, each applying a pressure up to 120 mm Hg for 2–3 s before deflating. This sequence is continued at a rate of three cycles per minute throughout the treatment session.

The physiologic effects of IPC are thought to be a consequence of three mechanisms: an increase in the arteriovenous pressure gradient; reversal of vasomotor paralysis; and enhanced release of nitric oxide.[14]

**Stem Cell Therapy**

Stem cell therapy is another developing technique to induce therapeutic angiogenesis. Autologous stem cell therapies have used bone marrow mononuclear cells or endothelial progenitor cells obtained from bone marrow harvest or, less frequently, from circulating peripheral blood stem cells. Our institute was a part of multicenter trial phase I, phase II and the results were encouraging.

Tateishi-Yuyama et al.[15] in a randomized prospective trial, showed that injection of bone marrow–derived mononuclear cell injections resulted in a significant increase in ABI and tcPO$_2$ compared with controls. Sharma et al.[16] in a pilot study showed that injection of autologous platelet-rich plasma can provide efficient treatment for pain and healing of ischemic ulcers in TAO (Buerger’s disease) patients.

**Amputation**

The aim of early detection of patients with PAD is to avoid amputation. In spite of aggressive treatment, some of the patients may end up in amputation either due to advanced ischemia or because of gross sepsis. The level of amputation is decided on the basis of presence of pulse, popliteal pressure and transcutaneous oxygen perfusion at the level of amputation. The major task after amputation is proper rehabilitation and make them independent and integrated with the society. Advances in the prosthesis have made this job much easier.
TYPE A LESIONS

- Unilateral or bilateral stenoses of CIA
- Unilateral or bilateral single short (<3 cm) stenosis of EIA

TYPE B LESIONS

- Short (<3 cm) stenosis of infrarenal aorta
- Unilateral CIA occlusion
- Single or multiple stenoses totaling 3–10 cm involving the EIA not extending into the CFA
- Unilateral EIA occlusion not involving the origins of internal iliac or CFA

TYPE C LESIONS

- Bilateral CIA occlusions
  - Bilateral EIA stenoses 3–10 cm long not extending into the CFA
  - Unilateral EIA stenosis extending into the CFA
  - Unilateral EIA occlusion that involves the origins of internal iliac and/or CFA
  - Heavily calcified unilateral EIA occlusion with or without involvement of origins of internal iliac and/or CFA

TYPE D LESIONS

- Infrarenal aortoiliac occlusion
- Diffuse disease involving the aorta and both iliac arteries requiring treatment
- Diffuse multiple stenoses involving the unilateral CIA, EIA, and CFA
- Unilateral occlusions of both CIA and EIA
- Iliac stenoses in patients with AAA requiring treatment and not amenable to endograft placement or other lesions requiring open aortic or iliac surgery origins of internal iliac and/or CFA

TASC classification of femoropopliteal lesions

TYPE A LESIONS

- Single stenosis <10 cm in length
- Single occlusion <5 cm in length

TYPE B LESIONS

- Multiple lesions (stenoses or occlusions), each <5 cm
  - Single stenosis or occlusion <15 cm not involving the infrageniculate popliteal artery
  - Single or multiple lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass
  - Heavily calcified occlusion <5 cm in length
  - Single popliteal stenosis

TYPE C LESIONS

- Multiple stenoses or occlusions totaling >15 cm with or without heavy calcification
- Recurrent stenoses or occlusions that need treatment after two endovascular interventions

TYPE D LESIONS

- Chronic total occlusions of CFA or SFA (>20 cm, involving the popliteal artery)
- Chronic total occlusion of popliteal artery and proximal trifurcation vessels

Figure 2: Transatlantic Inter Society Consensus classification of aortoiliac lesions

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