

UNIT NO. 6

CLINICAL SEQUELAE OF ATHEROTHROMBOSIS:
PERIPHERAL ARTERY DISEASE

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ABSTRACT

Peripheral arterial disease (PAD) is the manifestation of athero-thrombosis in the lower limb vessels giving rise to symptoms of obstruction like claudication, ulceration or gangrene. Because these patients often have concomitant disease in the cardiac and cerebro-vascular bed, they also carry significant risk of dying from cardiovascular events. Therefore it is essential that patients diagnosed with PAD should be given anti-platelet therapy to reduce these events.

The treatment of PAD depends on its presentation. Patient with claudication only can be treated conservatively with exercise and control of risk factors. However, patient with gangrene and rest pain, or patient with acute ischemia will need revascularization urgently.

INTRODUCTION

Peripheral arterial occlusive disease (PAD) is the manifestation of atherothrombosis in the lower-limb blood vessels, giving rise to symptoms of obstruction such as claudication and complications that include limb loss.

Scope of the Problem*Prevalence*

PAD is common, being present in almost 20% of people over 70 years of age.¹ Furthermore, being a disease of the elderly, its prevalence will increase as our population ages.

Morbidity and outcome

PAD is a manifestation of systemic atherothrombosis, and hence carries significant risk of death from a cardiovascular event. The five-year mortality rate for PAD patients is close to 30%, as patients die from co-morbid conditions of coronary artery disease (CAD) and cerebrovascular disease.¹ In fact, among patients with severe and symptomatic PAD, only 25% survive for 10 years or longer.²

However, despite its prevalence and the associated mortality risk from cardiovascular events, PAD receives little attention and is often under-diagnosed, with no pharmacological treatment given.

DISEASE SYNDROMES

The varied presentation of PAD can be broadly divided into three clinical syndromes:

1. Functional ischaemia
2. Chronic critical ischaemia
3. Acute ischaemia.

Functional ischaemia

In this group of patients, the restriction in the peripheral blood flow is mild and the flow is sufficient for muscle at rest. However, blood flow cannot increase in response to exercise, giving rise to claudication pain in the specific muscle unit. This pain subsides with resting.

This is considered a benign stage of PAD, because data have shown that the majority of patients do not need interventional treatment:

- o In three quarters of cases, the patient remains stable and symptoms may improve with exercise alone;
- o Only 16% experience a worsening of their claudication symptoms;
- o Just 7% need bypass surgery;
- o Less than 4% undergo limb amputation;
- o Approximately 1.4% of patients with intermittent claudication progress to ischaemic rest pain and/or gangrene (higher among smokers and diabetics).³

Chronic critical ischaemia

This occurs when blood flow is so reduced that it is insufficient for the requirements of resting tissue. Patients complain of pain in the forefoot even at rest. This is often experienced at night when sufferers are supine and gravity cannot enhance the limited flow. In more severe cases, tissue loss occurs and patients develop non-healing ulcers and gangrene. If left untreated, the majority of these patients will end up with amputations.

Two criteria define chronic critical limb ischaemia:

1. Recurring rest pain that persists for more than 2 weeks and requires regular analgesia, with an ankle systolic pressure ≤ 50 mm Hg, or a toe pressure of ≤ 30 mmHg, or both.
2. Ulceration or gangrene of the foot or toes with similar haemodynamic parameters.

Acute ischaemia

Acute limb ischaemia is defined as any sudden decrease or worsening in limb perfusion producing a potential threat to limb viability. It can be caused by an embolus from a distant source or thrombosis of a pre-existing atheromatous plaque. With an embolus, the obstruction tends to lodge in

non-diseased vessels with no collateral formation; this tends to produce sudden and severe limb-threatening ischaemia. By contrast, ischaemia from thrombosis occurs in a vessel with pre-existing disease and collateral vessels have often already formed; the presentation is therefore less sudden and severe.

CLINICAL PRESENTATION

Causes for the clinical presentation

The list of causes for the clinical presentation is as follows:

- o Embolism
 - κ Left atrium in patients with atrial fibrillation
 - κ Mural thrombus after myocardial infarct
 - κ Prosthetic and diseased heart valves
 - κ Aneurysm or atheromatous stenosis
- o Local causes
 - κ Thrombosis of an atheromatous plaque
 - κ Dissecting aneurysm.

The classical presentation can be described by the 'six Ps': pain, pallor, pulselessness, paralysis, paraesthesia and poikilothermia.

Unlike functional and chronic ischaemia, acute limb ischaemia is an emergency and requires immediate attention to prevent limb loss.

Pain

The majority of PAD patients present with a painful leg. Each of the syndromes mentioned above presents with different kinds of pain, and by getting a detail picture of the pain, one can make a diagnosis in 90% of cases even before clinical examination. A small group of patient will present with a non-healing ulcer or gangrene.

There are three types of ischaemic pain:

1. Claudication pain
2. Rest pain
3. Acute ischaemic pain.

Claudication pain

This is the most common presentation of PAD. It is defined as intermittent pain of a certain muscle unit, precipitated by fixed amount of exercise and relieved by stopping the activity. The important diagnostic points to remember are:

- o The pain is in the muscle unit and not in the joint or skin. The muscle unit involved depends on the site of the disease. A patient with aorto-iliac disease will complain of proximal muscle ache or pain in the thigh and hip muscles, whereas someone with femoro-popliteal disease will have calf muscle pain
- o The discomfort is precipitated by walking a certain fixed distance, depending on the severity of the disease, and is reproducible
- o The pain is completely relieved just by stopping the walking.

Pseudo-claudication (neurogenic claudication) is the term used to describe calf pain in patients with spinal stenosis. The important differentiating points are:

- o The pain is induced by anything that increases lumbar lordosis rather than just ambulation (prolonged standing or walking)
- o Pain is relieved by sitting down or stooping. It may require 15 to 20 minutes before the pain subsides
- o There is often an associated symptom of numbness in the foot.

Ischaemic rest pain

Ischaemic pain experienced even at rest indicates critically severe PAD. The characteristics of this pain are:

- o It is experienced at rest, especially at night when the patient lies supine
- o It is in the forefoot and not in a muscle unit like the calf
- o The patient can obtain relief by putting the leg to a dependent position. This can be done by dangling the feet over the bed or by getting up and walking.

Acute ischaemic pain

If a patient complains of severe and sudden onset of pain of the leg associated with coldness, paraesthesia and progressive paralysis, acute ischaemia should be suspected until proven otherwise.

ASSESSMENT OF PATIENTS WITH PAD

History

Assess the affected part

Assess the affected part on the 'six Ps': pain, pallor, pulselessness, paralysis, paraesthesia and poikilothermia.

Look for involvement in other vascular beds

- o Cerebrovascular symptoms, such as transient ischaemic attack and stroke
- o Ischaemic heart disease
- o Mesenteric ischaemia present with postprandial abdominal pain 30 to 60 minutes after eating; this may last for 2 to 3 hours.

Assess risk factors

Look for presence of the following risk factors:

- o Family history
- o Smoking
- o Diabetes mellitus
- o Hypertension
- o Hypercholesterolaemia.

Physical examination

Assess the general state of blood vessels. Specifically:

- o Look for aneurysm dilatation especially in the abdomen
- o Auscultate for bruits in the carotid, abdominal and femoral area

- o Feel for all the pulses. Weakness of pulses in the femoral region associated with hip claudication indicates aortoiliac disease. Absent popliteal and pedal pulse with calf claudication suggest superficial femoral disease.

Look for evidence of advanced ischaemia, specifically:

- o Evidence of atrophy in the muscle, skin and nails, suggesting a chronic insufficiency
- o Coldness to touch
- o Color changes; a poor capillary refill is an early sign of ischaemia; the presence of Buerger's sign (pallor of the sole on elevation and rubor on dependency) suggest a very severe state of ischaemia
- o Tissue loss.

The presence of a painful ischaemic ulcer and gangrene are evidence of critical limb ischemia.

Noninvasive testing

Ankle-brachial index

Please refer to module III for a detailed description of this topic.

Segmental pressure

- o The measurement of pressure gradient across the leg can indicate the level and significance of arterial occlusive disease
- o This is done by having appropriately sized pneumatic cuffs on the upper thigh, below the knee and above the ankle. Pressure is measured at the ankle as each cuff is inflated and deflated
- o A pressure gradient of >20 mmHg between the cuff levels indicates significant disease between the cuffs.

Toe pressure

Measurement of toe pressure is done using a toe cuff applied at the proximal phalanx, and the signal is picked up using a small photoplethysmograph. It has the following advantages:

- o Provides accurate assessment of distal circulation
- o Not influenced by calcification in pedal vessels, as seen in diabetics
- o Normal toe pressures are 90 to 100 mmHg
- o Toe pressure of less than 30 mmHg suggests critical limb ischaemia
- o Useful in predicting healing of foot lesions.

Duplex scanning

Duplex scan uses a combination of B mode ultrasound and pulsed Doppler spectral analysis of flow velocity pattern to assess the anatomy of the vessel and its disease, as well as assessing its haemodynamic significance by measuring its flow. Duplex scanning is non-invasive and very cost effective, but the main disadvantage is that it is very dependent on the operator.

Other test that are less commonly used includes transcutaneous oxygen tension, laser Doppler, plethysmography and penile/brachia index.

Invasive testing

Digital subtraction angiography (DSA) is the gold standard for the study of peripheral arteries. However, it is an invasive procedure and should not be used as a screening tool for patients with claudication. It should be reserved for patients in which an endovascular procedure or surgical bypass is contemplated.

Computed tomography or magnetic resonance angiography with 3D reconstruction has slowly gain popularity as software has improved. They provide sufficient details to match DSA but without the invasiveness and risk of DSA.

MANAGEMENT OF PAD

The management of PAD has three primary aims:

1. To reduce morbidity and mortality from coronary and cerebrovascular events.
2. To alleviate the symptoms of claudication and improve lifestyle and quality of life.
3. To prevent limb loss in critical ischaemia by prompt and relevant intervention.

Medical management

Cardiovascular risk factor modification

1. Elimination of cigarette smoking: Every effort must be made to get PAD patients to stop smoking. This not only reduces the risk of death from myocardial infarction and cerebrovascular events, it also slows the progression of PAD. It has been shown that cessation of smoking increases ankle pressure and improves exercise tolerance.³
2. Control of hyperlipidaemia: Several trials have shown that lipid lowering is associated with a beneficial effect on lower limb atherosclerosis, including stabilisation or regression of atherosclerosis in the leg.⁴ The aim of the therapy is to obtain serum low-density lipoprotein cholesterol levels <100 mg/dL (2.6 mmol/L) and serum triglyceride levels <150 mg/dL (1.7 mmol/L).⁵
3. Control of diabetes mellitus: Intensive control of diabetes has not been shown to prevent the progression of PAD, but it will definitely help in controlling infections and improve healing.
4. Hypertension control: Hypertension is major contributing factor to PAD, causing stress on the arterial wall. There is no data showing that controlling hypertension will improve claudication, but controlling blood pressure will reduce events from other vascular beds.

Antiplatelet therapy

- o Antiplatelet therapy in patients with cardiovascular disease has been shown in meta-analysis studies to reduce serious vascular events (defined as nonfatal myocardial infarction, nonfatal stroke or vascular death)^{6,7}
- o Aspirin is recommended for patients with PAD, to reduce morbidity from cardiovascular events
- o Other antiplatelet agents, including ticlopidine, can be

used although this agent carries a substantial risk of thrombocytopenia and neutropenia (about 2.3 %) and thrombotic thrombocytopenic purpura

- o Clopidogrel, an antiplatelet agent in the same group as ticlopidine (a thienopyridine), was shown in the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) trial to be superior to aspirin in the reduction of cardiovascular events. This has prompted the FDA to approve clopidogrel for secondary prevention of atherosclerotic events in patients with PAD.⁸

Treatment of claudications

The majority of patient with claudication will either improve or remain stable over time. Only about 5% to 10% will require intervention in five years, and the majority of these patients are those who continue to smoke or who are diabetic. Therefore, the initial treatment for claudication is usually non-operative.

(1) Exercise

Regular exercise is key:

- o Patients with claudication often stop walking regularly for fear of pain. This only makes the situation worse. They should be encouraged to do regular walking exercise. Randomised trials have shown that exercise is as effective as bypass or angioplasty and meta-analysis has showed that exercise increases maximal walking distance of up to 179 m⁹
- o Patients should walk until they experience the claudication, rest until it subsides and then continue the cycle. This should go on for about 45 to 60 minutes per day and up to three to five times per week. After a few months, this will increase metabolic adaptation and improve collateral formation. The patient will be able to walk further.

(2) Drugs

There are many drugs that have been used as pharmacological therapy to improve claudication. There are sufficient data to show that pentoxifyline, cilostazol and naftidrofuryl improve the symptoms of claudication. Ginkgo biloba is also popular but it has yet to be evaluated in large clinical trials. Chelation therapy has been shown not to be useful for claudication.

Pentoxifyline is the first FDA-approved drugs for use in intermittent claudication. It is a rheologic agent that reduces blood viscosity by improving red blood cell membrane flexibility and inhibiting platelet aggregation. It has been shown to increase claudication distance.¹⁰

Cilostazol is a new agent with favourable effects on intermittent claudication. Results have been well described in a large population of non-diabetic and diabetic patients.^{10,11} Studies have shown that 12 weeks of cilostazol use reduces claudication severity and increases walking distance by as much as 40% when compared to placebo.^{10,11}

Interventional therapy

Indications

Indication for interventional therapy for PAD is listed as follows:

- o Severe claudication: Patients whose claudication symptoms affect their lifestyle in that they are not able to carry on their usual occupation, or they are not able to enjoy their leisure activities
- o All patients with critical limb ischaemia require early intervention to prevent limb loss
- o All patients who present with acute ischaemia need immediate anticoagulation and intervention to remove the obstruction.

Endovascular treatment

Minimal invasive treatment is the catchphrase that permeates all field of medicine. This is no different in PAD.

Angioplasty with or without stenting has gained in popularity. It is favoured for obstruction in the bigger vessels, like the iliac and femoral artery, but is less useful for small tibial vessels. The stenosis should be <5 cm in length and preferably not a complete obstruction. Best results are seen with stenosis less than 2 cm in length.

Initial success can be achieved in >90% of cases. It has a respectable 5 year patency of 90% for aorto-iliac vessels and 70% for infra-inguinal vessels.

Percutaneous thrombolysis of embolus and thrombosis has also gain importance in the treatment of acute ischaemia.

Bypass Surgery

Surgeries in the form of bypass still play a major role in PAD. Indication for surgery includes:

- o Patients who have a long and diffuse disease of the lower limb arteries
- o Patients who have failed endovascular treatment
- o Diseases of tibial vessels where endovascular therapy is not suitable.

Embolectomy is performed in acute ischaemia to remove embolus or thrombus from the acutely occluded vessels.

Bypass performed using either prosthetic or vein graft is used to improve blood supply to the affected leg:

- o Aorto-bifemoral bypass – for bilateral disease of the iliac arteries
- o Femoro-popliteal bypass – for disease in the superficial femoral arteries
- o Femoro-tibial or popliteal-tibial bypass – for multilevel disease involving tibial vessels in the calf.

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LEARNING POINTS

1. Patient with peripheral arterial disease has a significant risk of dying from a cardiovascular event.
 2. Once diagnosed, patient with PAD should be started on antiplatelet therapy.
 3. Most patient with intermittent claudication can be treated non-surgically with regular exercise and control of risk factors.
 4. Claudication pain occurs in muscle unit like the calf or thigh whereas restpain is usually at the forefoot.
 5. Pentoxifyline, Cilastazol and Naftidrofuryl are useful in improving symptoms of claudication.
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