Peripheral Arterial Disease and Critical Limb Ischemia

Nomenclature and Definitions

The term “peripheral arterial disease” (PAD) broadly encompasses the vascular diseases caused primarily by atherosclerosis and thromboembolic pathophysiological processes that alter the normal structure and function of the aorta, its visceral arterial branches, and the arteries of the lower extremity. Peripheral arterial disease is the preferred clinical term that should be used to denote stenotic, occlusive, and aneurysmal diseases of the aorta and its branch arteries, exclusive of the coronary arteries. (Hirsch et al, 2006)

PAD is characterized by a partial or complete failure of the arterial system to deliver oxygenated blood to peripheral tissue. Atherosclerosis is by far the most common etiology of PAD. However, several other processes can lead to the clinical syndrome like arterial entrapment, thrombosis, adventitial cyst, embolism, fibromuscular dysplasia, dissection, trauma, vasculitis and vasospasm. (Gardner & Afaq, 2008)

Critical limb ischemia (CLI) is a manifestation of PAD that describes patients with typical chronic ischemic rest pain or patients with ischemic skin lesions, either ulcers or gangrene. The term CLI should only be used in relation to patients with chronic ischemic disease, defined as the presence of symptoms for more than 2 weeks. (Norgren et al, 2007)

The ankle brachial blood pressure index (ABI), defined as the systolic blood pressure measured at the ankle divided by the systolic blood pressure measured in the arm during supine rest, is the most widely used quantitative measure to determine the presence and severity of PAD. An abnormal ABI value of ≤ 0.90 is generally considered to be the best reference standard of identifying PAD, whereas normal values range between 0.9 to 1.3. (Gardner & Afaq, 2008)

Epidemiology and Natural History

Lower extremity PAD is a common syndrome that affects a large proportion of most adult populations worldwide. Peripheral arterial disease can be present in subclinical forms that can be detected by use of sensitive vascular imaging techniques, which may reveal early manifestations of arterial disease before it is detected by either limb-pressure measurements or clinical symptoms. When so defined, as, for example, by measurement of the intimal-medial thickness (IMT) in the carotid or femoral artery, early forms of PAD are easily detected in populations at risk. (Hirsch et al, 2006)

The prevalence of asymptomatic PAD based on objective testing has been evaluated in several epidemiologic studies and is in the range of 3% to 10%, increasing to 15% to 20% in persons over 70 years. It can be estimated that for every patient with symptomatic PAD there are another three to four subjects with PAD who do not meet the clinical criteria for intermittent claudication. (Norgren et al, 2007)

Intermittent claudication (IC) is usually diagnosed by a history of muscular leg pain on exercise that is relieved by a short rest. The prevalence

of IC would appear to increase from about 3% in patients aged 40 to 6% in patients aged 60 years. A surprising finding in population screening studies is that between 10% and 50% of patients with IC have never consulted a doctor about their symptoms. (Norgren et al, 2007)

CLI populations are difficult to study, with large numbers of patients lost to follow-up or dying in longitudinal studies, leading to incomplete data sets. (Norgren et al, 2007)

A subgroup of PAD patients fall outside the definition of either claudication or CLI. These patients have severe PAD with low perfusion pressures and low ankle systolic pressures, but are asymptomatic. They are usually sedentary and, therefore, do not claudicate, or they may have diabetes with neuropathy and reduced pain perception. These patients are presumed vulnerable to develop clinical CLI. The natural history of this subgroup of severe PAD is not well characterized, but outcomes of excess mortality and amputation would be expected. The term ‘chronic subclinical ischemia’ has been ascribed to this subgroup. (Norgren et al, 2007)

The prognosis of patients with lower extremity PAD is characterized by an increased risk for cardiovascular ischemic events due to concomitant coronary artery disease and cerebrovascular disease. These cardiovascular ischemic events are more frequent than ischemic limb events in any lower extremity PAD cohort, whether individuals present without symptoms or with atypical leg pain, classic claudication, or CLI. (Hirsch et al, 2006)

Evidence suggests that the progression of the underlying PAD is identical whether or not the subject has symptoms in the leg. There is nothing to suggest that the risk of local deterioration, with progression to CLI, is dependent on the presence or absence of symptoms of intermittent claudication. (Norgren et al, 2007)

Although PAD is progressive in the pathological sense, its clinical course as far as the leg is concerned is surprisingly stable in most cases. It is estimated that only about a quarter of patients with IC will ever significantly deteriorate. This symptomatic stabilization may be due to the development of collaterals, metabolic adaptation of ischemic muscle, or the patient altering his or her gait to favor non-ischemic muscle groups. This clinical stability is relevant to the patient's perception of their severity of claudication. When these patients have a comprehensive assessment of their actual functional status, measured walking distance does progressively deteriorate over time. (Norgren et al, 2007)

Natural history studies of claudication document that few patients progress to CLI. Many patients who present with CLI are asymptomatic prior to its development. (Norgren et al, 2007)

Pathophysiology:

Lower extremity PAD may be caused by atherosclerotic, thromboembolic, inflammatory, or aneurysmal disease; by trauma, adventitial cysts, or entrapment syndromes; or by congenital abnormalities. The major cause of lower extremity PAD is atherosclerosis. Risk factors for atherosclerosis such as cigarette smoking, diabetes, dyslipidemia, hypertension, and hyperhomocysteinemia increase the likelihood of developing lower extremity PAD. (Hirsch et al, 2006)

Regardless of the etiology, the pathophysiology of CLI is a chronic and complex process that affects the macro-vascular and micro-vascular systems, as well as surrounding tissues. Initially, the body response to ischemia is angiogenesis, or capillary sprouting, thereby promoting the enlargement of pre-existing collaterals to aid in the increase of blood flow to the critically

ischemic limb. These responses fail to supply the necessary amount of blood flow and oxygen to the limb, causing arterioles in patients with CLI to become maximally vasodilated and insensitive to provasodilatory stimuli. This phenomenon, referred to as vasomotor paralysis, is thought to be the result of chronic exposure to vasorelaxing factors. Together, these changes lead to edema, a major concern in these patients. In addition, patients with CLI often hold their limbs in a dependent position to alleviate ischemic rest pain; combined with impaired vasomotor control, this leads to further aggravation of the edema. Edema increases the hydrostatic pressure within the distal portion of the limb, compressing already compromised capillaries and impairing diffusion of nutrients to the tissue. (Varu et al, 2010)

Risk Factors for Peripheral Arterial Diseas:

1. Race:

The National Health and Nutrition Examination Survey in the United States found that an ABI ≤0.90 was more common in non-Hispanic Blacks (7.8%) than in Whites (4.4%). Such a difference in the prevalence of PAD was confirmed by the recent GENOA (Genetic Epidemiology Network of Arteriopathy) study, which also showed that the difference was not explained by a difference in classical risk factors for atherosclerosis. (Norgren et al, 2007)

2. Gender:

The prevalence of PAD, symptomatic or asymptomatic, is slightly greater in men than women, particularly in the younger age groups. In patients with IC, the ratio of men to women is between 1:1 and 2:1. This ratio increases in some studies to at least 3:1 in more severe stages of the disease, such as chronic CLI. Other studies have, however, shown a more equal distribution of PAD between genders and even a predominance of women with CLI. (Norgren et al, 2007)

3. Age:

There is striking increase in both the incidence and prevalence of PAD with increasing age. (Gardner & Afaq, 2008), (Norgren et al, 2007)

4. Smoking:

Smoking is deleterious for patients with PAD, and a clear dose-response relationship has been shown in these patients. (Willigendael et al, 2004)

The progress of PAD is more aggressive in smokers and vascular interventions are less successful. Cessation of smoking reduces both the risk of severe symptoms and the risk of death in vascular complications. (Jörneskog, 2012)

Cigarette smoking is the most important risk factor for the development and progression of PAD. The amount and duration of tobacco use correlate directly with the development and progression of PAD. Smoking cessation increases long-term survival in patients with PAD. (Marso & Hiatt, 2006)

5. Diabetes Mellitus:

Peripheral arterial occlusive disease is 2–4 times more common in patients with diabetes than in patients without diabetes. (Beckman et al, 2002)

6. Hypertension:

Hypertension is associated with all forms of cardiovascular disease, including PAD. However, the relative risk for developing PAD is less for hypertension than diabetes or smoking. (Norgren et al, 2007)

7. Dyslipidemia

Although some studies have shown that total cholesterol is a powerful independent risk factor for PAD, others have failed to confirm this association. It has been suggested that cigarette smoking may enhance the effect of hypercholesterolemia. There is evidence that treatment of hyperlipidemia reduces both the progression of PAD and the incidence of IC. An association between PAD and hypertriglyceridemia has also been reported and has been shown to be associated with the progression and systemic complications of PAD. (Norgren et al, 2007)

8. Inflammatory Markers:

Some recent studies have shown that C-reactive protein (CRP) was raised in asymptomatic subjects who in the subsequent five years developed PAD compared to an age-matched control group who remained asymptomatic. (Ridker et al, 2001), (Norgren et al, 2007)

9. Hyperviscosity and Hypercoagulable States:

Raised hematocrit levels and hyperviscosity have been reported in patients with PAD, possibly as a consequence of smoking. Increased plasma levels of fibrinogen, which is also a risk factor for thrombosis, have been associated with PAD in several studies. Both hyperviscosity and hypercoagulability

have also been shown to be markers or risk factors for a poor prognosis. (Norgren et al, 2007)

10. Hyperhomocysteinemia:

It is reported that hyperhomocysteinemia is detected in about 30% of young patients with PAD. (Norgren et al, 2007)

11. Chronic Renal Insufficiency:

There is an association of renal insufficiency with PAD, with some recent evidence suggesting it may be causal. (Norgren et al, 2007)

Clinical Presentations of CLI:

Critical limb ischemia (CLI) is a clinical definition involving a spectrum of clinical features to describe chronic and severe compromise in limb perfusion that results in failure to meet the basal metabolic needs. It is ordinarily manifested by the presence of rest pain, with or without trophic skin changes or tissue loss, including ischemic ulceration and/or ischemic gangrene with appropriate documentation of circulatory impairment. Typically, narcotic medications are required for analgesia. (White, 2010) (Cao et al, 2009)

PAIN:

Ischemic rest pain, the main feature of patients with CLI, is typically described as burning pain, usually worse in the distal foot and in the toes and usually most severe at night. Rest pain is generally intolerably severe, aggravated by elevation, and relieved with dependency, presumably

resulting from the increase in arterial pressure from gravity in a limb with a nonfunctioning venoarteriolar reflex due to ischemia. The pain occurs or worsens with reduction of perfusion pressure: leg elevation with loss of the supplemental effects of gravity on blood flow. In diabetic patients the superficial pain sensation may be altered and they may experience only deep ischemic pain such as calf claudication and ischemic rest pain. In the most severe cases of CLI, rest pain is continuous, with episodes lasting minutes to hours but with constant diffuse pain remaining in between. Often the pain cannot be adequately relieved from foot dependency and responds only to opiates. (Cao et al, 2009)

ULCERS AND GANGRENE

Further progression of tissue hypoxia ultimately leads to tissue ulceration and gangrene. (Figure 1) However, in many patients, particularly diabetic patients with diabetic neuropathy, CLI does not progress from rest pain to tissue loss but the initial presentation is with a neuroischemic ulcer or gangrene. On the basis of literature, there are significant differences at this stage of CLI between patients with or without diabetes. The former have been recognized and distinguished in a separate subcategory of CLI in the TASC “diabetic foot ulcers”. Non diabetic gangrene and ulcers usually affect the digits or the pressure points (the heel in bedridden patients) and may extend to the distal parts of the foot. Gangrene is usually caused by a minor local trauma, local pressure (fitting shoes), or use of local heat. Gangrenous tissue can shrink and form a scar leading to mummification and spontaneous amputation. However, necrotic tissue may also be infected with spreading of tissue loss. (Cao et al, 2009)

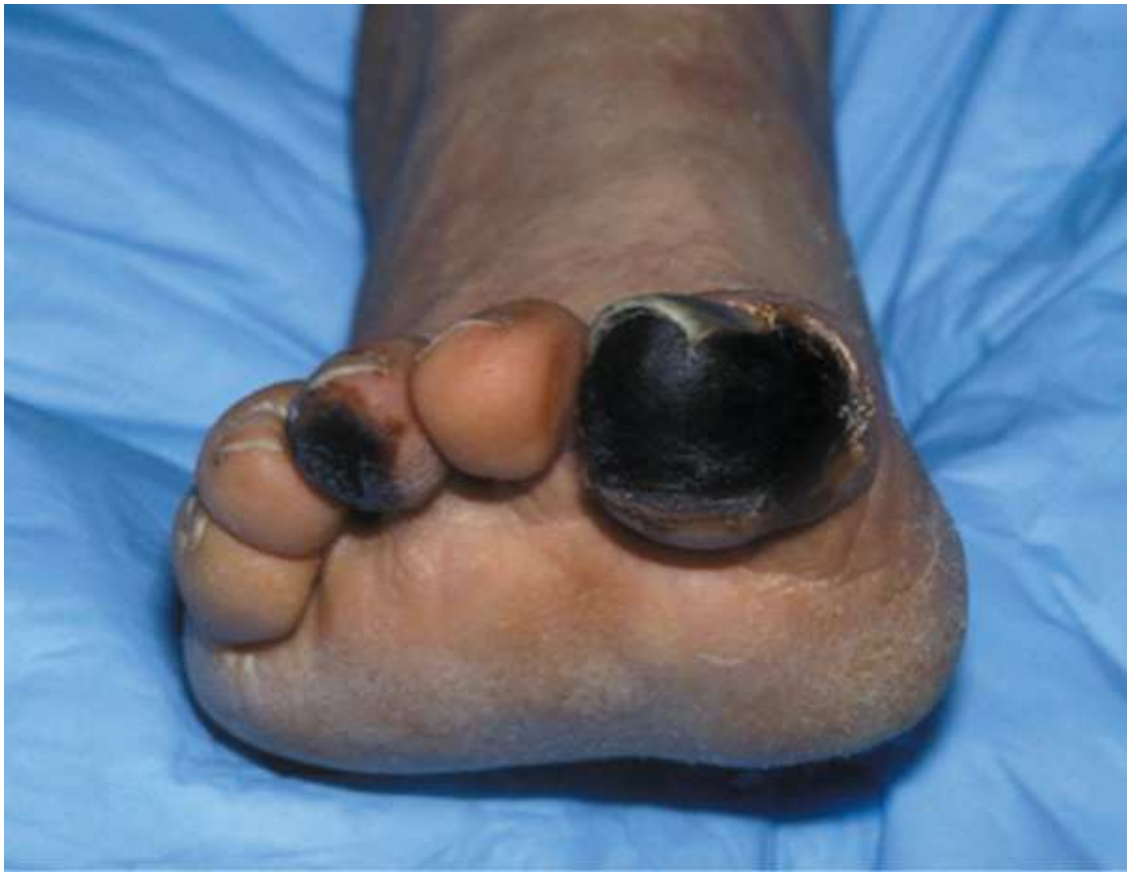


Figure 1 : Ischemic gangrene in a patient with critical limb ischemia. **(Topol et al, 2006)**

Diabetic Foot

It has been estimated that about 15% of people with diabetes will develop foot ulcers during their lifetime and about 14% to 24% will require amputation. Diabetic foot complications are the most common cause of nontraumatic lower extremity amputations in the world, but also the most preventable when detected early and treated appropriately. Early identification of the patient at risk and preventive foot care could prevent up to 85% of diabetic amputations. The most common pathway associated with the development of diabetic ulcers includes peripheral neuropathy; approximately 30% of diabetics have mild to severe forms of nerve damage. Loss of protective sensation leads to insensate foot more vulnerable to repetitive trauma especially at pressure points. Motor nerve defects and limited joint mobility can cause structural foot deformities further predisposing the patient to foot lesions. Because of autonomic neuropathy, loss of sweating, dry fissured skin, and increased arteriovenous shunting occur. Healing requires a greater increase in perfusion than needed to maintain intact skin. Although the majority of diabetic ulcers are neuropathic, the TASC classifies diabetic foot ulcerations in three broad categories, which are ischemic, neuroischemic, and neuropathic. (Cao et al, 2009)

SUBCRITICAL LIMB ISCHEMIA

It has been recently suggested that there is a subgroup of patients with CLI in whom severely reduced circulation to the foot does not manifest as rest pain, ischemic ulceration, or ischemic gangrene. Those patients are said to have “chronic subcritical limb ischemia (CSLI)”. It has been recognized that

patients with peripheral arterial disease do not usually go through gradual progression from claudication to advanced stages of CLI because many develop CLI without warning. At least part can be explained by this asymptomatic stage, CSLI, in patients who do not ambulate for various reasons and therefore do not present with claudication or attribute their limited walking ability to other conditions such as arthritis or cardiopulmonary compromise. At this stage foot skin is intact; however, they do not have sufficient perfusion to heal foot wounds, and should they receive minor trauma, the wound would result in nonhealing ischemic lesions and evident CLI with limb threat. These patients need to be discovered before these events precipitate in order to apply preventive foot care to avoid foot infection, control risk factors to improve mortality outlook, and to have regular follow-up and attentive care. However, there is currently no evidence to support the usage of aggressive revascularization procedures at early CSLI, and those patients can be efficiently managed by medical treatment to prevent progression of the disease. (Cao et al, 2009)

Classification schemes for CLI:

The main purpose of defining and grading chronic arterial limb ischemia is to predict outcome and to standardize reporting practices. Many classification systems for grading the severity of chronic arterial occlusive disease have been suggested. In the case of critical limb ischemia (CLI), attempts at a precise definition based on clinical grades of classification systems have been problematic. Current CLI definitions have been criticized for being unclear, and not able to predict outcome accurately. (Norgren et al, 2007)

There are two major classifications based on the clinical presentations: the Fontaine classification, and the Rutherford classification.

Rutherford			**Fontaine**	
Clinical	**Category**	**Grade**	**Clinical**	**Stage**
Asymptomatic	0	0	Asymptomatic	I
Mild claudication	1	I	Mild claudication	IIa
Moderate claudication	2	I	Moderate to severe claudication	IIb
Severe claudication	3	II		
Ischemic rest pain	4	III	Ischemic rest pain	III
Minor tissue loss	5	IV	Ulceration or gangrene	IV
Major tissue loss	6			

Table 1: Classification of peripheral arterial disease: Fontaine's stages and Rutherford's categories

Vascular Laboratory for CLI:

Objective and reliable assessment of perfusion in the foot is of utmost importance in the management of CLI. Several different methods have been used and should be available in a modern vascular laboratory, which should be validated. All methods have their own strengths and pitfalls and the clinician should be aware of these. None of the methods is satisfactory as a single tool, but information gained from several methods should be combined and interpreted together with the clinical picture. (Venermo et al , 2012)

There is a clear need to assess both macro- and microcirculation in the context of critical limb ischaemia, especially in diabetics.

Table 2: Assessment of impaired perfusion in a diabetic foot applicable for CLI

Microvascular:

- Laser Doppler techniques
- TcPO2
- Skin perfusion pressure

Macrovascular

- Ankle systolic blood pressure
- Ankle/brachial index
- Toe systolic blood pressure
- Toe/brachial index
- Segmental blood pressure
- Pulse volume recording
- Toe flow velocity waveform

Anatomical

- Duplex ultrasound imaging
- Computed tomography angiography
- Magnetic resonance angiography
- Digital subtraction angiography

(Venermo et al, 2012)

ANKLE-BRACHIAL INDEX (ABI)

The Ankle-brachial index (ABI) is the ratio of systolic blood pressure at the ankle and systemic blood pressure measured from the brachial artery when the patient is at a supine position. Blood pressure at the ankle level is measured using a hand-held continuous-wave Doppler ultrasound probe from both the dorsalis pedis artery and the posterior tibial artery. The higher ankle value is divided with the higher of the systolic arm blood pressures.(Figure 2) ABI-measurement is easy, non-invasive, relatively quick and inexpensive. ABI measurement has been proven to be reliable when performed by vascular experts, family physicians and nurses. ABI can be measured at any practice equipped with Doppler and a blood pressure cuff, and it should be available in all primary health care units. Most often, normal ABI is defined to be 0.9–1.3. Values below 0.9 predict peripheral arterial disease in 95% of the cases, while those higher than 1.3 predict mediasclerosis and non-compressible vessels at ankle level, and the ABI is pseudohypertensive. (Venermo et al , 2012)

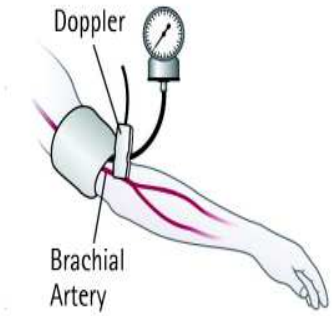
PULSE VOLUME RECORDING (PVR)

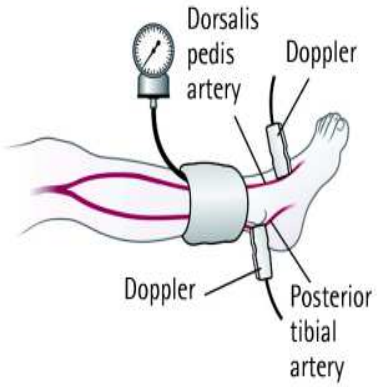
Segmental pulse volume recordings at various levels of the leg have traditionally been used in primary non-invasive diagnostics of vascular disease and the assessment of the level of the occlusive lesions. Today, duplex has made PVR unnecessary in this sense. However, PVR deserves a mention here as it may be used as an additional measure when estimating the reliability of toe pressure and ABI measurements or as a quick method for detecting graft patency or a major change after endovascular treatment. (Venermo et al, 2012)

1. Patient should rest supine in a warm room for at least 10 minutes before testing.
2. Place blood pressure cuffs on both arms and ankles as illustrated, then apply ultrasound gel over brachial, dorsalis pedis, and posterior tibial arteries.
3. Measure systolic pressures in the arms
   - use Doppler to locate brachial pulse
   - inflate cuff 20 mm Hg above last audible pulse
   - deflate cuff slowly and record pressure at which pulse becomes audible
   - obtain 2 measures in each arm and record the average as the brachial pressure in that arm
4. Measure systolic pressures in ankles
   - use Doppler to locate dorsalis pedis pulse
   - inflate cuff 20 mm Hg above last audible pulse
   - deflate cuff slowly and record pressure at which pulse becomes audible
   - obtain 2 measures in each ankle and record the average as the dorsalis pedis pressure in that leg
   - repeat above steps for posterior tibial arteries
5. Calculate ABI

$$\text{Right ABI} = \frac{\text{highest right average ankle pressure (DP or PT)}}{\text{highest average arm pressure (right or left)}}$$

$$\text{Left ABI} = \frac{\text{highest left average ankle pressure (DP or PT)}}{\text{highest average arm pressure (right or left)}}$$





Site	1st reading	2nd reading	average	Site	1st reading	2nd reading	average
Left brachial				Right brachial			
Left dorsalis pedis				Right dorsalis pedis			
Left posterior tibial				Right posterior tibial			

Figure 2: Measurement of Ankle/Brachial pressure Index **(http://quzugaho37.blog.com/2014/01/18/ankle-brachial-index-exam/)**

TOE PRESSURE (TP):

Toe pressure and TcPO2 measurements are the most widely used noninvasive methods in assessing foot perfusion and wound healing potential. The rationale behind measuring TP is that it is the most distal pressure representing the macrocirculation that can be measured, and the toe arteries are less prone to mediasclerosis. Thus it might represent a suitable alternative to ABI in diabetic patients with false high ABI records. There are three principally different methods for detecting flow in the toes – the mercury strain-gauge, photoplethysmography (PPG) and laser Doppler (LD), the latter two being the ones still in use. After the detection of flow, a suitably sized cuff is inflated to a pressure at which the signal is no longer detectable. The pressure where the signal returns during deflation is recorded as the toe systolic pressure. Recent European guidelines on diabetic foot management have acknowledged the problem of TP reliability especially in diabetics and have raised the level of probable wound healing from the previous 30–50 mmHg to 50–55 mmHg . In non-diabetics a cut-off value of 30 mmHg has been used for rest pain. (Venermo et al, 2012)

TRANSCUTANEOUS PARTIAL OXYGEN PRESSURE (TcPO2):

Transcutaneous oxygen pressure measurement (TcPO2) reflects the metabolic state of the underlying skin and is considered to reflect the tissue healing potential. It is based on the amount of oxygen that is diffused from the capillaries through the epidermis to a measuring electrode at a certain point. The electrode heats the underlying tissue in order to create local

hyperaemia. The oxygen is reduced at the cathode of the electrode and produces a current that is proportional to the partial pressure of oxygen (PO2). Due to the fact that it measures the perfusion in capillaries and arterioles, it is very sensitive to vasospastic errors. The advantage of TcPO2 is that it may be measured at several points of the skin. It may be measured in the proximity of the ulcer or any other area of interest and is thus more modifiable than toe pressure measurement. The areas of different angiosomes may be measured separately. An ulceration of the foot in diabetes will generally heal if the TcPO2 is > 50 mmHg. Healing is usually severely impaired when TcPO2 is < 30 mmHg. (Venermo et al, 2012)

COLOR DUPLEX IMAGING:

The improved resolution of duplex imaging has made this diagnostic modality a suitable alternative to contrast angiography in some patients. A significant advantage of this noninvasive modality is that it yields both anatomic and blood flow information, providing an assessment of the hemodynamic effect of arterial occlusive lesions without the use of nephrotoxic contrast agents. Current devices offer significantly improved image quality. Combined with an assessment of peak systolic velocity ratios, duplex imaging can characterize arterial anatomy and detect hemodynamically significant lesions with an accuracy similar to that of conventional contrast angiography. (White, 2010)

CDI is employed in the surveillance of arterial bypass grafts and is increasingly being used as a first-line investigation for patients presenting to vascular clinics. Arterial calcification can interfere with CDI. Medial sclerosis, frequently seen in the iliofemoral and infrageniculate arteries in

diabetes, typically has a uniformly high signal on B-mode ultrasound, but generally permits flow analysis. However, waveform analysis proximal and distal to these areas can indicate whether significant disease is present. Dampened waveforms with reduced peak velocity indicate the presence of significant stenotic disease proximal to the point of analysis. Further, there is the potential to fail to localize significant arterial disease proximally, particularly in obese individuals and to miss distal disease in small vessels so preventing accurate anatomical mapping. Obese individuals with type 2 diabetes are potentially a challenge for this modality. (Williams, 2009)

Computed Tomographic Angiography (CTA):

With improvements in computed tomography technology, CTA has become another frequently used imaging modality for viewing even the small distal tibial vessels. The studies are obtained quickly, requiring no more than a few minutes to scan from the proximal abdominal aorta to the feet, which minimizes issues related to patient noncompliance. (White, 2010)

Despite these excellent results, there are limitations to the widespread use of CTA for the evaluation of lower extremity ischemia. Of major concern is the requirement for an intravenous bolus of more than 100 mL of iodinated contrast in the average adult. This high contrast load limits the use of CTA to patients with normal renal function, unless medical necessity indicates otherwise. Additionally, in the presence of significant amounts of arterial wall calcium, especially in smaller vessels, cross-sectional images must be carefully reviewed and compared with the reconstructed three-dimensional images. Small arteries that are occluded with calcified plaque may be

misconstrued as patent. Finally, metal artifact may obscure images in patients with metal implants or surgical clips in their legs. (White, 2010)

CTA, by combining the luminal information provided by DSA with the cross-sectional view supplied in traditional axial CT, offers the advantages of both those imaging technologies, thereby offering additional visualization of vessel wall and extraluminal processes, and anatomic relationships with adjacent structures. Short bolus durations associated with short scan durations, however, require accurate scan time setting. (Giampietro & van den Berg, 2009)

Magnetic Resonance Angiography

Gadolinium-enhanced magnetic resonance angiography (MRA) is gaining acceptance for the evaluation of patients with lower limb ischemia because it can visualize the entire arterial tree, including pedal vessels, without the use of arterial puncture or standard ionic contrast agents. (White, 2010)

MRA is not completely free of patient-related difficulties, however. Patients with newly placed metallic implants are frequently not candidates for exposure to the magnetic field. Others may require sedation because of claustrophobia or difficulty lying flat for a long time. Additionally, although gadolinium is only mildly nephrotoxic, it may adversely affect renal function in patients with preexisting renal insufficiency. Therefore, MRA should be incorporated into a thoughtful diagnostic and therapeutic plan to ensure that the potential benefit of the information obtained outweighs the small risk of complication and discomfort. (White, 2010)

Finally, the presence of turbulent flow can result in signal loss, which may result in an overestimation of the degree of stenosis. Another pitfall that should be mentioned when considering MRA is the evaluation of tortuous arteries that may appear occluded if they are not carefully included in the plane of imaging. Finally, MRA does not offer visualization of bony landmarks for assisting surgeons in planning operations. (Giampietro & van den Berg, 2009) (Williams, 2009)

Diagnostic angiography:

Conventional contrast intra-arterial subtraction angiography continues to be the most commonly used imaging modality for planning bypass surgery and percutaneous interventions. Complete visualization of the arterial tree is accomplished easily and rapidly. This is especially true of the inflow segments, the infrarenal aorta and iliac arteries, and the renal and visceral vessels, which frequently are not well visualized by duplex imaging. (White, 2010)

Because there is no image loss induced by arterial wall calcium, angiography is complementary to color duplex imaging in patients in whom the distal vasculature cannot be completely evaluated. Angiography should be undertaken in patients with PAD only when the need for and possibility of intervention have been established. (White, 2010)

Risks of angiography include the risks of arterial puncture, which may result in compromise of the distal circulation due to induction of thrombosis, embolism, or dissection, or in pseudoaneurysm formation, as well as the risks associated with contrast administration. Risks associated with contrast

administration include allergic reactions, hypotension, systemic vasodilatation, stroke, and convulsions. Renal insufficiency may also be precipitated via contrast administration. This risk may be minimized via adequate hydration and the use of nonionic low-osmolarity contrast agents. (Williams, 2009)

TASC Classification of infrainguinal PAD:

Nowadays, TASC is of limited use in decision making in treatment of infrainguinal disease. This due to rapid development of endovascular techniques and devices. Furthermore, the use of the TASC classification may be problematic due to considerable inter-individual differences in interpretation. (Norgren et al, 2007), (Kukkonen et al, 2010), (Zimmermann et al, 2010)

However, since the wide spread use of the TASC classification system in the past decade, most studies used this method to classify lesions under investigation. (Setacci C. et al, 2009)

The new TASC femoropopliteal criteria reflect the fact that increasingly complex disease can be managed using endovascular techniques. TASC type A lesions are suitable candidates for endovascular therapy (ET); TASC type D lesions necessitate surgery, owing to ET's prohibitive failure rate; and TASC types B and C lesions can be treated using either endovascular or surgical revascularization, depending on the clinical scenario. There is some evidence that in patients with high-grade disease (e.g., TASC type C or D) who are facing imminent limb loss but are not candidates for surgical reconstruction, endovascular reconstruction may be beneficial. (Sadek et al, 2009)(Table 3)

Table 3: Femoropopliteal TASC II classification. (Norgren et al, 2007)

Type	Lesion Characteristics
A	Single stenosis≤10 cm Single occlusion ≤5 cm
B	Multiple stenoses or occlusions, each ≤5 cm Single stenosis or occlusion ≤15 cm not involving infrageniculate popliteal artery Single or multiple lesions in the absence of continuous tibial vessels to improve inflow for tibial bypass Heavily calcified occlusion ≤5 cm Single popliteal stenosis
C	Multiple stenoses or occlusions totaling >15 cm with or without heavy calcification Recurrent stenoses or occlusions that need treatment after two endovascular interventions
D	Chronic occlusion of common or superficial femoral artery >20 cm or involving popliteal artery Chronic occlusion of popliteal artery and proximal trifurcation vessels

Consensus regarding the effectiveness of ET for infrapopliteal arterial occlusive disease is limited. This is reflected by the TASC guidelines, which do not delineate specific anatomic criteria for infrapopliteal ET. These guidelines state that infrapopliteal angioplasty and stenting should be reserved for limb salvage therapy; there is insufficient evidence to recommend their use for the treatment of intermittent claudication. The only specific recommendation is that in a patient with CLI and medical co-morbidities who is being treated for infrapopliteal occlusion, ET may be attempted if in-line flow to the foot can be re-established. The TASC guidelines also mention that failed angioplasty usually does not preclude subsequent bypass. Therefore, as is the case with femoropopliteal disease, if a patient is at high risk for surgical bypass and is facing imminent limb loss, PTA may be considered to avoid amputation. (Schneider, 2005)

Table 4: Trans-Atlantic Inter-Society Consensus (TASC) I classification for infrapopliteal lesions.

Classification	Lesion characteristics
TASC A	Single stenosis <1 cm long
TASC B	Multiple focal stenoses<1 cm long or 1 or 2 stenoses <1 cm involving the trifurcation
TASC C	Stenoses 1-4 cm long, occlusion 1-2 cm long, or extensive stenosis involving trifurcation
TASC D	Occlusion >2 cm long or diffusely diseased

(Dormandy et al, 2000)

Treatment of CLI:

The primary goals of the treatment of CLI are to relieve ischemic pain, heal (neuro) ischemic ulcers, prevent limb loss, improve patient function and quality of life, prolong survival, modify risk factors and improve quality of life. A primary outcome would be amputation-free survival. In order to achieve these outcomes, most patients will ultimately need a revascularization procedure. Other components of treatment of patients with CLI are medical interventions to control pain and infection in the ischemic leg, prevention of progression of the systemic atherosclerosis, and optimization of cardiac and respiratory function. For some CLI patients with severe co-morbidities or a very limited chance of successful revascularization, a primary amputation may be the most appropriate treatment. Cardiovascular risk factor control is mandatory in CLI patients as well as in all PAD patients. (Norgren et al, 2007)

MEDICAL TREATMENT

Pain Control:

Pain management is essential in improving function and quality of life. The hallmark of CLI is ischemic rest pain and painful ulceration. Pain is usually located to skin and possibly bone structures. Pain control is a critical aspect of the management of these patients. Ideally, relief of pain is achieved by reperfusion of the extremity. However, while planning the revascularization, adequate pain control must be a goal of management in all patients. (Norgren et al, 2007)

Management of Ulcers:

Prior to a revascularization procedure the ulcer can be treated with non-adherent gauze and should be off-loaded if there is an increase in pressure or shear stress. Once perfusion is improved, adequate off-loading becomes more important as the increase in blood flow may not compensate for the repetitive tissue trauma due to poorly fitted shoes. (Norgren et al, 2007), (Pedrini, 2003)

Treatment of Infection:

Local infection is a severe complication of a neuroischemic ulcer, as it tends to run a more severe course and should be treated urgently. The infection should be identified as early as possible and its level of involvement assessed and aggressively treated. Severe foot infections in diabetic patients are usually polymicrobial with gram positive cocci, gram negative rods and anaerobic organisms. Once the clinical diagnosis of an infection is made and cultures of the wound obtained, empiric antibiotic treatment should be initiated immediately. (Norgren et al, 2007)

Risk Factor Modification:

As in all patients with diabetes, those with concomitant CLI should have optimization of glycemic control. Diabetic patients with a neuro-ischemic foot ulcer frequently have a poor health status. Factors that can negatively affect wound healing such as cardiac failure or poor nutritional status should be evaluated and treated appropriately. (Norgren et al, 2007) (Cao et al, 2009)

Patients with vascular disease should be screened carefully for diabetes. HbA1c should be checked. Strict glycemic control with a target HbA1c level of less than 6.5% in all patients with PAD is recommended on the basis of data showing a nearly 60% reduction in microvascular complications. (Cao et al, 2009)

Smoking is an independent risk factor for the development of CLI. Patients who stop smoking reduce their risk for developing CLI or major amputation. The goal for patients with CLI who smoke is complete cessation. A successful tobacco cessation strategy includes both behavioral therapy and pharmacotherapy. (Cao et al, 2009)

Pharmacotherapy for critical limb ischemia:

Prostanoids:

Prostanoids prevent platelet and leukocyte activation and protect the vascular endothelium, which could play a role in the management of CLI. These drugs are administered parenterally over several weeks. Side effects include flushing, headache, and hypotension of a transient nature. (Norgren et al,2007)

Vasodilators (PENTOXIFYLLINE AND CILOSTAZOL):

Direct-acting vasodilators are of no value, as they will primarily increase blood flow to non-ischemic areas. While pentoxifylline and cilostazol have been advocated in claudicants, neither is used in the treatment of CLI. (Cao et al, 2009)

Antiplatelet drugs:

There is no evidence that these drugs would improve outcomes in CLI. However, as in all patients with PAD, antiplatelet drugs do reduce the risk of systemic vascular events. (Cao et al, 2009)

According to ACC/AHA 2005 guidelines for management of PAD, all patients undergoing revascularization for CLI should be placed on antiplatelet therapy , and this treatment should be continued indefinitely. This is supposed to maximize the benefit of revascularization and to minimize the risk of cardiovascular ischemic events *(Level of Evidence: A)* (Hirsch et al, 2006)

Antiplatelet therapy should be started preoperatively and continued as adjuvant pharmacotherapy after an endovascular or surgical procedure. *(Level of Evidence: A)* (Norgren et al, 2010)

Anticoagulants:

Unfractionated heparin is frequently used as prophylaxis and as adjuvant treatment to vascular surgical procedures, but has not been tried for symptoms of CLI. (Cao et al, 2009)

Following revascularization, when autogenous grafts are used, patients might recieve warfarin as an adjuvant therapy to improve the patency rate. This may be accompanied by a risk of hemorrhage and this decision must be made on an individual patient basis. (Norgren et al, 2007)

Revascularization:

The natural history of CLI is such that intervention is indicated to salvage a useful and pain-free extremity. The treatment chosen depends upon the pre-morbid condition of the patient and the extremity as well as estimating the risk of intervention based on co-morbid conditions and the expected patency and durability of the reconstruction. In CLI, multi-level disease is frequently encountered. Adequate inflow must be established prior to improvement in the outflow. After revascularization, ulcer healing may require adjunctive treatments that may be best achieved in collaboration between the vascular specialist and specialists in foot care. (Norgren et al, 2007)

Surgical Therapy

For a long time, surgical therapy has been considered the gold standard for treatment of limb-threatening ischemia and, in selected cases, disabling claudication. Overall, two techniques predominate in the surgical treatment of peripheral vascular disease: endarterectomy and bypass. Endarterectomy involves removal of the diseased intima and innermost media, leaving behind a smooth arterial surface. It is especially well suited to the treatment of short segmental or ostial lesions such as those seen at the carotid or aortic bifurcations. Bypass, as the name implies, involves the routing of blood flow around a stenotic or occluded arterial segment using a conduit, typically either autogenous vein or prosthesis [polytetrafluoroethylene (PTFE) or Dacron]. Operative therapy is recommended for patients with long segment and multisegmental disease, especially if total occlusion is present. Aortofemoral bypass is associated with a low operative mortality (2–3%)

and an 80–85% 5-year patency rate. Iliac reconstruction is generally recommended for isolated unilateral iliac arterial disease, which can also be treated by a femoral artery to femoral artery crossover bypass graft. Infrainguinal arterial reconstruction is associated with a 60–80% 5-year patency rate, with better outcome noted for autogenous vein conduit than for prosthetic bypasses. (AbuRahma, 2007)

Endovascular Therapy

Endovascular therapy is an evolving modality in which devices are introduced directly into the vascular lumen via an open or percutaneous approach. The stenotic areas are then addressed via several techniques:

Balloon angioplasty, in which a balloon is expanded across a stenotic area, thus fracturing the plaque and expanding the arterial lumen via a "controlled dissection."

Atherectomy, in which a specially designed catheter is used to shave a portion of the plaque from inside the vessel lumen.

Stenting, or stented endovascular grafting, involving the placement of an expandable metal stent across the stenotic area.

The application of percutaneous endovascular therapy for arterial occlusive disease of the lower extremities continues to increase. The long-term results of endovascular therapy are expected to improve with the progression of the technology supporting these therapeutic interventions. Overall, the initial technical success rates for open surgical procedures and percutaneous endovascular therapy are somewhat similar; however, surgery

frequently provides greater long-term patency. On the other hand, angioplasty is often associated with lower morbidity and mortality rates, and late failure of percutaneous endovascular therapies can often be treated successfully with percutaneous reinterventions. (AbuRahma, 2007)

Salvage procedures:

Limb salvage after revascularization is defined as preservation of some or all of the foot. An attempt at a foot salvage procedure should take place after a revascularization procedure has been performed if possible. A waiting period of at least 3 days has been suggested, this allows for sufficient time for the restoration of perfusion and for demarcation to occur. The level of adequate circulation, extent of infection, if any and remaining function of the foot are factors considered when choosing the level of a foot salvage procedure. Foot salvage procedures can be divided into two categories. The first category involves amputation of some part of the foot. The second category of foot salvage involves the debridement of the wounds, including excision of bone. Foot salvage procedures, short of amputation, that can be used in the revascularized foot include arthroplasty, metatarsal head excision and calcanectomy. (Norgren et al, 2007)

Amputation:

Major amputation (above the ankle) in CLI is necessary and indicated when there is overwhelming infection that threatens the patient's life, when rest pain cannot be controlled, or when extensive necrosis has destroyed the foot. Using these criteria, the number of major limb amputations should be limited. Primary amputation is defined as amputation of the ischemic lower extremity without an antecedent attempt at revascularization. Amputation is

considered as primary therapy for lower limb ischemia only in selected cases. Revascularization of the lower extremity remains the treatment of choice for most patients with significant arterial occlusive disease. Unreconstructable vascular disease has become the most common indication for secondary amputation, accounting for nearly 60% of patients. Secondary amputation is indicated when vascular intervention is no longer possible or when the limb continues to deteriorate despite the presence of a patent reconstruction. Persistent infection despite aggressive vascular reconstruction is the second most common indication. (Norgren et al, 2007)

Many amputations can be prevented and limbs preserved through a multi-armed, limb-salvage treatment of ischemic necrosis with antibiotics, revascularization and staged wound closure that may necessitate the use of microvascular muscle flaps to cover major tissue defects. On the other hand, and very importantly, amputation may offer an expedient return to a useful quality of life, especially if a prolonged course of treatment is anticipated with little likelihood of healing. Non-ambulatory elderly patients with CLI represent a particularly challenging group. These patients frequently have flexion contractures that form from the prolonged withdrawal response to the pain. Aggressive vascular reconstruction does not provide these patients with a stable and useful limb, and primary amputation is a reasonable option. Therefore, the important issue is to identify a subgroup of CLI patients better served by an amputation than attempts of revascularization. Technical aspects, foot wound healing issues and co-morbidities of the patients should be considered. (Norgren et al,2007)

CONSERVATIVE TREATMENT:

Gangrenous and infected toes can be successfully amputated in patients with good circulation. Extensive debridements and partial foot amputations will also usually heal in such patients if all infected and necrotic tissue is excised. Such procedures will result in patients regaining an effective walking status. Amputation of one or more gangrenous or ulcerated toes or limited debridements may also sometimes result in a healed foot in patients without distal pulses and substantial arterial occlusive disease [e.g., an occluded superficial femoral artery (SFA)]. Determination of moderately good collateral circulation by ankle-brachial indices or pulse volume recordings may be helpful in predicting such healing, but sometimes in patients with borderline circulation, a trial of such local procedures is warranted before proceeding with a major effort at revascularization. If healing is not thereby achieved, the revascularization is clearly justified. In addition, some patients with critical ischemia as manifest by mild ischemic rest pain and/or limited gangrene or ulceration can be successfully managed conservatively with good foot care, antibiotics, analgesics, and limited ambulation . A trial of such conservative treatment is particularly indicated in patients who might not tolerate revascularization procedures because of major comorbidities. Long periods of palliation and occasional healing of small ulcerations and patches of gangrene may take place in a limited proportion of such patients with critical ischemia. (Veith et al, 2009)