ABSTRACT

The pathophysiology of CLI is complex and involves both macrovascular and microvascular pathology. Therefore it is not surprising that therapeutic modalities are multifold, spanning many health care specialties and requiring substantial institutional infrastructure to provide optimal patient care. The future of CLI treatment is as exciting as it is challenging. There is increasing focus on optimal wound care and prevention, adherence to proven medical therapies, improving revascularization results with novel endovascular and surgical techniques and devices, and ongoing investigation into promising therapies like therapeutic angiogenesis.

Keywords

- Critical
- Ischemia
- Recent
- Management

INTRODUCTION

Critical limb ischemia (CLI) is the most severe form of peripheral arterial disease (PAD) and represents approximately 1% of the total number of patients with PAD ***(Dormandy et al., 2000).***

The international definition of CLI is any patient with chronic ischemic rest pain, ulcers, or gangrene attributable to objectively proven arterial occlusive disease ***(Weitz et al., 1996).***

Critical limb ischemia (CLI) is a severe condition of perfusion insufficiency in the lower extremities, commonly leads to peripheral artery occlusive disease (PAOD). CLI is often caused by atherosclerosis related to hypertension, diabetes, or smoking; to date, no effective medical therapy is available for CLI ***(Powell et al., 2008).***

The mean annual incidence of CLI is 340 to 1000 per million in USA. As would be expected given the systemic nature of atherosclerosis, severe PAD is often associated with advanced coronary artery and cerebrovascular disease. CAD has been estimated to be present in approximately half of patients with CLI ***(Feringa and Norgren et al., 2007).***

This strong association results in an exceedingly high mortality from MI and stroke among patients presenting with CLI, significantly higher than those with PAD alone. A review of major series reporting the fate of patients with CLI noted that Up

to 40% of CLI cases have lead to major amputation and up to 26% of cases died within 1 year of diagnosis ***(Duval et al., 2014)***.

Most ultrasonography and angiography measurements during early stages of atherosclerotic disorders manifest normal blood circulation. Although neuropathy and atherosclerotic peripheral arterial diseases can coexist in the lower limb, neuropathy may mask the symptoms and signs of CLI, thus confounding diagnosis ***(Stanton et al., 2010).***

Even with aggressive local wound care, patients with severe limb ischemia and chronic ulceration who do not undergo revascularization often progress to amputation, with the likelihood of amputation increasing as the ABI decreases ***(Marston et al., 2006).***

Revascularization to reestablish continuous in-line flow to the pedal arch represents the preferred treatment for patients with limb-threatening ischemia. Options for revascularization include surgery, endovascular intervention, and 'hybrid therapy', a combination of surgical and endovascular therapy ***(Norgren et al., 2007).***

Amputation is indicated after failed attempts at revascularization, if the patient is unfit or unable to undergo revascularization, in the presence of extensive tissue loss or infection, and in patients who do not ambulate. According to the TASC guidelines, 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 recovery ***(Norgren et al., 2007).***

The traditional methods of assessing outcomes and quality of care in patients with CLI such as survival and limb salvage is increasingly noted to be inadequate, and functional outcomes, such as maintenance of ambulatory status and independent living status, achievement of healed wound status, avoidance of repeat hospitalizations, and interventions, are proposed as more meaningful parameters in these patients. A better understanding of such patient-oriented measures of success will have a profound impact on decision making for the treatment of lower extremity PAD ***(Nehler et al., 2004).***

Patients who present with CLI are often consumed by their disease and are condemned to a course of prolonged recovery with multiple re-operations and hospital admissions ***(Holtzman et al., 2015)***.

AIM OF THE WORK

Aim of the work is to discuss recent trends in management of critical lower limb ischemia in the endovascular era.

ANATOMICAL ASPECTS

Peripheral Arterial Anatomy

The abdominal aorta bifurcates into bilateral common iliac arteries. The common iliac arteries divide into the internal iliac arteries, which supply the pelvis, and continue on as the external iliac arteries. The external iliac arteries, after passing under the inguinal ligament, become the common femoral arteries. The profunda femoris artery branches off the common femoral artery as the superficial femoral artery continues. As the superficial femoral artery passes into the popliteal fossa, it is renamed the popliteal artery. Upon exit from this fossa, the popliteal artery trifurcates into the anterior tibialis artery, which distally is the dorsalis pedis artery, the posterior tibialis artery, and the peroneal artery ***(Robert et al., 2012)***.

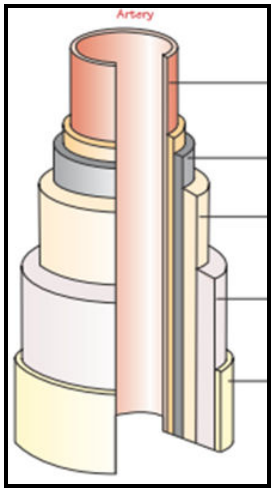
Applied Anatomy:

It is well recognized that atherosclerosis is a focal disease manifested throughout the arterial vasculature. Differences in flow parameters within various vascular beds account for the localization of atherosclerosis, which tends to occur at sites of low shear stress, turbulence, and oscillating flow ***(Stary, 2000).***

Histological anatomy:

The endothelium is an organ with autocrine, paracrine, and endocrine functions that serve to regulate blood vessel tone and thrombogenicity. The endothelium synthesizes an array of

factors that regulate vascular tone (e.g., nitric oxide [NO], hyperpolarizing factors, prostaglandins, endothelin, angiotensin II) and interactions with blood elements (e.g., adhesion molecules, thrombomodulin, plasminogen activators), which all work in balance to maintain vascular homeostasis.



(1): Histological anatomy of arterial wall ***(Vascular and Endovascular Surgery at a Glance, 2014)***

Endothelial dysfunction is regarded as the earliest manifestation of vessel injury and is present before histologic evidence of atherosclerosis ***(Alfred Bollinger et al., 2012).***

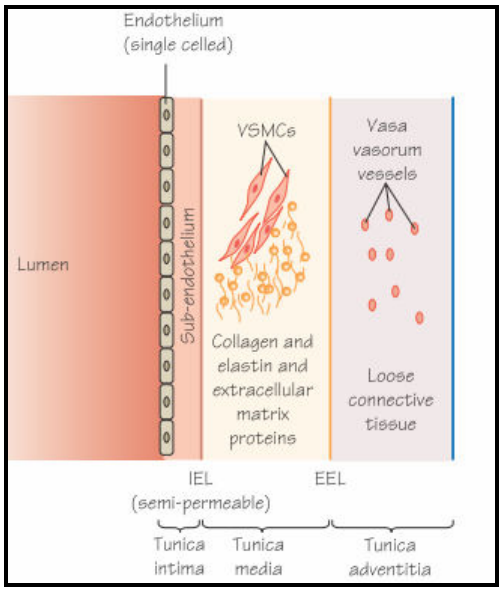


Figure (2): Histological anatomy of arterial wall ***(Vascular and Endovascular Surgery at a Glance, 2014)***.

The subendothelial space is particularly relevant in atherosclerosis because it is the location where atherogenic particles are retained and modified so that they can be taken up by macrophages and SMCs ***(Lieberman et al., 1996).***

PATHOPHYSIOLOGY

Pathophysiology of critical limb ischemia is characterized by three essential steps: macrovascular wall damage progressing to stenosis or occlusion, collateral development and phenomena at the microvascular level induced by the proximal changes.

Lower extremity occlusive PAD can be defined on the basis of anatomical or functional considerations. Anatomically it is defined as atherosclerotic arterial disease, while functionally it is defined as arterial narrowing, causing a mismatch between the oxygen supply and demand resulting in symptoms.

Pathology:

The term atheroma derives from the Greek athere, meaning "porridge" or "gruel"; sclerosis means "induration" or "hardening." A gruel-like color and consistency and induration or hardening exist to various degrees in different plaques, different disease stages and different individuals. In 1755, von Haller first applied the term atheroma to a common type of plaque that, on sectioning, exuded a yellow, pultaceous content from its core ***(Camejo et al., 1998).***

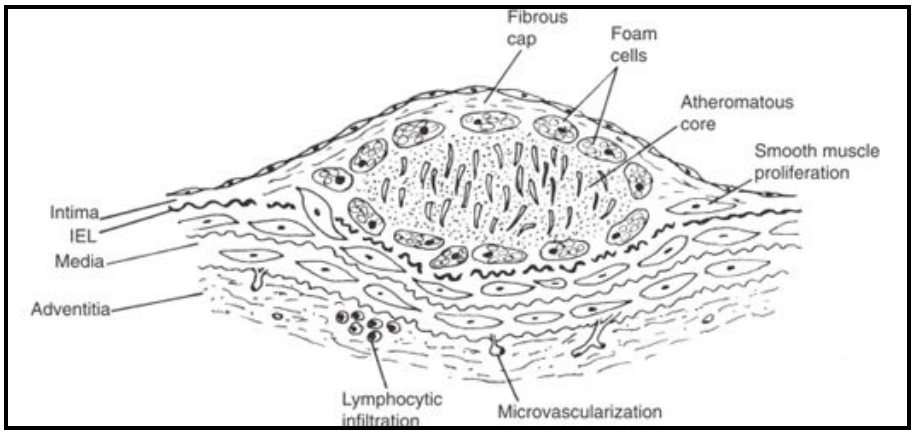


Figure (3): Atherosclerotic plaque ***(Vascular and Endovascular Surgery a Comprehensive Review, 1992)***.

Fatty streaks:

The first stages of atherosclerosis, fatty streaks, minimally raised yellow lesions, develop in characteristically vulnerable segments of the arterial tree. These lesions contain lipids deposited intracellularly in macrophages and in smooth muscle cells ***(Haimovici et al., 1990).***

Stary and colleagues defined initial fatty streaks and intermediate lesions of atherosclerosis as follows: ***(Haimovici et al., 1990).***

Type I lesions in children are early microscopic lesions, consisting of an increase in intimal macrophages and the appearance of foam cells.

Type II fatty streak lesions are grossly visible; in contrast to type I lesions, type II lesions stain with Sudan III or IV. Foam cells and lipid droplets appear in intimal smooth

muscle cells and heterogeneous droplets of extracellular lipids characterize type II fatty streaks.

Type III lesions are intermediate lesions, considered to be the bridge between the fatty streak and the prototypical atheromatous fibrous plaque, the type IV plaque Type III lesions occur in plaque-prone locations in the arterial tree at sites exposed to forces (particularly low-shear stress) promoting increased low-density lipoprotein (LDL) influx.

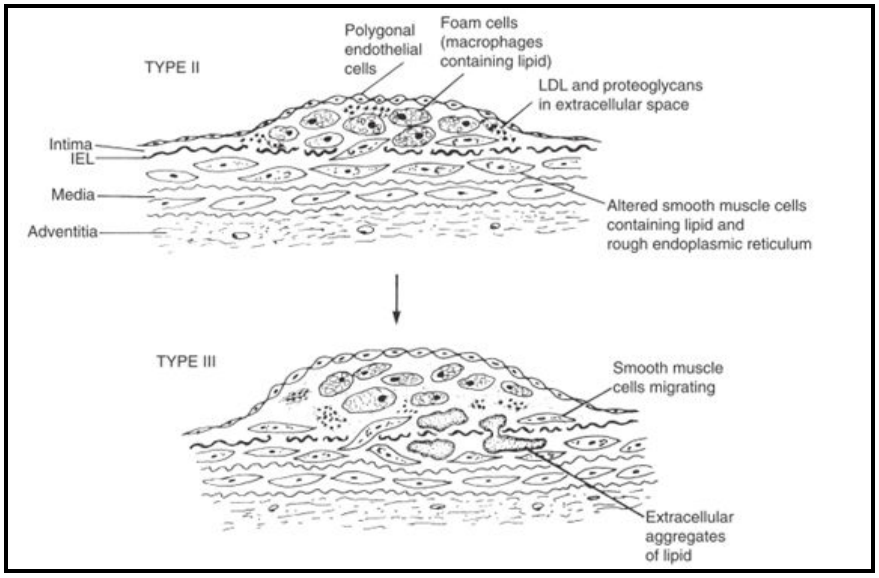


Figure (4): Atherosclerotic plaque ***(Vascular and Endovascular Surgery A Comprehensive Review, 1992).***

Fibrous Plaques:

The most common prototypical atherosclerotic lesion. These lesions are composed of large numbers of smooth muscle cells and connective tissue, which form a fibrous cap over an inner yellow (atheromatous) core. This soft core contains cholesterol esters, mainly cholesteryl oleate, likely derived

from disrupted foam cells. A second type of particle contains both free cholesterol and cholesterol linoleates. The early core is associated with vesicular lipids that are rich in free cholesterol ***(Glagov et al., 2013).***

CLI is usually caused by obstructive atherosclerotic disease; however, CLI can also be caused by atheroembolic or thromboembolic disease, vasculitis, in situ thrombosis related to hypercoagulable states, thromboangiitis obliterans, cystic adventitial disease, popliteal entrapment, or trauma. Regardless of the etiology, the pathophysiology of CLI is a chronic and complex process that affects the macrovascular and microvascular systems, as well as surrounding tissues ***(Guyton, Kemp, 1996).***

Table (1): Pathophysiology of critical limb ischemia ***(Glagov et al., 2013)***

Macrovascular changes	*Microvascular changes*
Atherosclerosis	Decreased nitric oxide production
Arterial stenosis	Increased reactive oxygen species
Angiogenesis	Increased peroxynitrite production
Arteriogenesis	Increased platelet activation
Increased VEGF	Increased leukocyte adhesion
Increased SDF-1	Microvascular thrombosis
Increased CXCR4 expression	Precapillary arteriole collapse
Vasomotor paralysis	Impaired oxygen exchange
Arterial remodeling	
Decreased wall thickness	
Decreased cross-sectional area	
Decreased wall-to-lumen ratio	
Increased skin perfusion	
Edema	

CXCR4, CXC chemokine receptor; *SDF-1,* stromal cell-derived factor-1; *VEGF,* vascular endothelial cell factor.

Initially, the body response to ischemia by angiogenesis, or capillary sprouting, as well as arteriogenesis, thereby promoting the enlargement of preexisting collaterals to aid in the increase of blood flow to the critically ischemic limb ***(Guyton and Kemp, 1996).***

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 ***(Hirsch et al., 2006).***

This phenomenon, referred to as vasomotor paralysis, is thought to be the result of chronic exposure to vasorelaxing factors in patients with diseased vessels. Further, blood vessels in patients with CLI have decreased wall thickness, decreased cross-sectional area, and decreased wall-to-lumen ratio compared with controls ***(Hirsch et al., 2006).***

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 ***(Hirsch et al., 2006).***

To complicate matters, microvascular dysfunction occurs in addition to the macrovascular changes. The endothelium protects the integrity of the blood vessel by modulating vascular tone, controlling vascular permeability and acting as an antithrombogenic barrier. Chronic ischemia from macroscopic disease leads to alterations in structure and function of endothelial cells and alterations in pressure unloading, which results in microcirculatory adaptations. This endothelial dysfunction leads to microthrombosis within the capillaries and exacerbates edema formation in the extremity ***(Hirsch et al., 2006).***

Furthermore, endothelial trauma results in increased free radical production, inappropriate platelet activation, and leukocyte adhesion, all of which lead to microthrombi formation ***(Hirsch et al., 2006).***

The result is that tissue oxygen exchange at the capillary level is impeded and less effective.

Many patients greatly benefit from restoration of flow, which is required for wound healing and limb salvage to occur. Yet simply correcting blood flow on a macrovascular level alone will not reverse the derangements discussed above. In fact, doing so initiates reactive hyperemia and a cascade of events that may further exacerbate an already complex problem ***(Tang et al., 2005).***

Thus, treatment of CLI must take into consideration a multitude of factors on a case-by-case basis.

Microvascular changes in critical ischemia:

Arteries:

Critical leg ischemia occurs when arterial stenosis increase proximal limb vascular resistance so severely that foot blood flow fails to meet the nutritive requirements of the resting limb. Chronic ischaemia may be compensated at two levels: (a) the development of collateral channels; and (b) reduction of peripheral limb vascular resistance by arteriolar vasodilatation. The onset of critical leg ischaemia implies the inadequacy of these compensations, and often results from the presence of multiple arterial occlusions at several levels, in critical collateral vessels, or in end-arteries ***(Tang et al., 2005).***

Rupture of an atherosclerotic plaque, possibly initiated by high shear stresses, can initiate haemorrhage within the plaque, thus exposing blood platelets to tissue factors as well as to pro-aggregatory adenosine diphosphate (ADP) released from red blood cells.

This platelet activation may trigger either:

A. Intra-plaque thrombus, with subsequent healing of the lesion by endothelialisation to produce a larger plaque
B. Non-occlusive luminal thrombus
C. Occlusive luminal thrombus.

Any of these events could precipitate critical ischaemia in the leg by increasing proximal limb arterial resistance to a