INTERVENTIONAL RADIOLOGY

Current review with evolving management strategies in critical limb ischemia

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Abstract

Critical limb ischemia represents the end stage of peripheral artery disease, which is associated with impaired quality of life and considerable morbidity and mortality. Economical impact of the disease is huge with a substantial burden on patients, healthcare providers, and resources. Varied therapeutic strategies have been employed in the management of these patients. These patients usually have complex multilevel occlusive arteriopathy with significant comorbidities, rendering surgical interventions undesirable in many cases. Recent therapeutic advances with evolving endovascular techniques and gene or cell-based therapies have the potential to dramatically change the therapeutic outlook in these patients.

Key words: Critical limb ischemia; peripheral artery disease; revascularization

Introduction

Critical limb ischemia (CLI) represents the most advanced form of peripheral artery disease (PAD) with high rates of cardiovascular events, amputations, and even death.^[1] Economical impact of the condition is immense with frequent hospital visits. Varied treatment strategies have been employed in the management of CLI with the primary aim of revascularization whenever feasible, though optimal revascularization strategy is still uncertain due to the lack of sufficient clinical evidence.^[2] Medical therapy is highly important for the optimization of cardiovascular risk factors as these factors are responsible for considerable mortality and morbidity. Further angiogenesis promoting therapies, such as gene or cell-based treatments appear promising emerging options in nonrevascularizable CLI.

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Definition

Use of CLI term in clinical practice is highly variable with different definitions in use, thus causing variable research reporting in this subset of patients. A uniform strict definition, including hemodynamic assessment is important to improve standardize reporting on CLI. Earlier definitions lack the hemodynamic assessment, as proposed by Fontaine *et al.* for the first time in 1954. As per current consensus definition, CLI is largely defined by a clinical constellation of symptoms including ischemic rest pain, ulcer, or gangrene in the context of objective hemodynamic evidence of manifest arterial insufficiency.^[3-5] As CLI represents the most advanced form of PAD, it is usually classified in the higher stages or grades of the Fontaine classification (stage III-IV)

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or the Rutherford classification (grades 4–6). The Society for Vascular Surgery has also created a CLI staging scheme recently, which is according to wound extent, ischemia, and degree of concomitant foot infection. This system defines four clinical stages of threatened limb and helps in risk stratification, guiding treatment strategy, and predicting the benefit of revascularization in these patients.^[6,7]

Epidemiology

PAD constitutes a common cause of vascular morbidity. It affects nearly 200 million people worldwide and is associated with 3 to 6-fold increased risk of cardiovascular mortality and morbidity as compared to patients without PAD.[8-10] CLI constitutes nearly 1% of the adult population and up to 10% of patients with PAD with an annual estimated incidence of 220–3500 new cases per million population.^[2,11-13] Moreover, approximately 5%-10% patients with asymptomatic PAD or intermittent claudication generally progress to CLI in a period of 5 years.^[2] CLI is associated with high mortality rates (nearly 16-20%, 50% and 70% at 1, 5, and 10 years, respectively),^[14-16] and the prognosis with respect to limb salvage is generally poor with amputation rates as high as 12% and 25% at 6 months and 1 year, respectively.^[17,18] Particularly, in no option CLI patients, 6 months amputation rates may range from 10% to 40%. Moreover, higher amputation rates have been shown in CLI patients (12%), 1 year after lower extremity bypass as compared to patients with claudication (1%).^[19] Coexistent atherosclerosis in other vascular territories is also commonly seen in these patients; significant coronary artery disease on angiograms in nearly two-third patients with CLI and significant carotid stenosis in approximately a quarter of patients with PAD,^[20,21] which is largely responsible for high mortality (13.4%, 19-25%, >60% at 6 months, 1 year and 5 years, respectively) and morbidity in these patients.^[17,22,23] There is high likelihood (annual rate 5% -7%) of adverse cardiovascular events (myocardial infarction, stroke, or death) in PAD patients, which is likely to be higher in patients with CLI.

Pathophysiology

CLI is generally caused by diffuse, progressive, multilevel, obstructive atherosclerosis. In minority of cases, CLI can also be secondary to hypercoagulable states, thromboembolism, vasculitis, Burger disease, trauma, cystic adventitial disease, and popliteal entrapment syndrome. The pathophysiology of CLI is a complex process and involves both macro- and micro-vascular changes leading to reduced perfusion to the extremities.^[18,24] Angiogenesis, an adaptive response occurs, thereby promoting enlargement of pre-existing collateral vessels to increase the blood flow to the critically ischemic limb. Distal arterioles further adapt to this chronic ischemic process by decreasing wall thickness, wall-to-lumen ratio, cross-sectional area, and with maximal vasodilatation,

thus producing a state of vasomotor paralysis, causing an orthostatic-dependent increase in the hydrostatic pressure, thereby producing distal edema. In addition to this, microvascular dysfunction occurs with endothelial damage resulting in inappropriate platelet activation, leukocyte adhesion, and increased free radical production, leading to microthrombi formation and causing impaired tissue oxygen exchange at the capillary level.

Diagnosis

CLI is largely a clinical diagnosis, which must be supported by objective hemodynamic criteria. These patients usually have diminished or absent distal pulses, thin/dry or shiny skin, loss of hair, dependent rubor or elevation pallor, or non-healing ulcer, and increased capillary refill time. Multiple noninvasive tests (including ankle pressure, toe pressure, pulse volume recordings, transcutaneous oxygen pressure, and Doppler evaluation) can be used to establish the diagnosis of CLI, assess foot perfusion, and predict wound healing. Ankle-brachial index (ABI) remains the simplest method, which provides important diagnostic and prognostic information in such patients.^[25] An ABI value less than 0.9 is indicative of PAD, while a value less than 0.4 is consistent with CLI.^[3] However, ABI assessment is limited in patients with renal failure or diabetes, where it may remain spuriously high or within the normal range, due to impaired vessel compressibility owing to medial calcinosis. In such cases, toe pressure readings may provide an optimal assessment of the distal perfusion.[26] Various imaging modalities (including Doppler, computerized tomography, or magnetic resonance angiography) have been used to assess the complete anatomical extent of the disease; however, digital subtraction angiography is still considered as the gold standard imaging evaluation, often providing a definitive treatment plan in these patients.^[27]

Management Options

Multiple treatment strategies [Table 1] have been employed in the management of CLI patients by different specialists involved in patient care, however, definite optimal revascularization remains uncertain. Therapeutic goals of treatment include optimization of coexistent cardiovascular risk factors, ischemic pain relief, ulcer healing, major amputation prevention, quality of life improvement, and patient survival. These aims can be achieved through optimal medical therapy, revascularization (surgical or endovascular), or amputation.

Medical therapy

Coexisting cerebrovascular and coronary artery disease accounts for considerable mortality and morbidity in CLI patients; hence, optimization of risk factors is of prime importance in the management of these patients. Medical therapy is primarily used to optimize these cardiovascular

Classification/Categorization	 Fontaine stage III-IV Rutherford grades 4-6 Staging based on wound extent, ischemia, and degree of concomitant foot infection (WIfI) ABI<0.4
Therapeutic goals	 Optimization of coexistent cardiovascular risk factors Ischemic pain relief Ulcer care & infection control Major amputation prevention Quality of life improvement and patient survival.
Management options	 Optimal medical therapy Smoking cessation Blood pressure control Strict glycemic control Revascularization (surgical or endovascular) Angiosome guidance Modified vascular access techniques including SAFARI, TAMI or pedal loop Amputation
Evolving treatment options	 Gene and cell based therapies Platelet rich plasma Deep venous arterialization Stem cell or growth factor eluting stents Bilayered stents (paclitaxel & growth factor) Advancements in atherectomy devices and angioplasty balloons (cryoplasty, laser or vibrational angioplasty)

Table 1: Key points with management options in critical limb

ABI = Ankle-brachial index, SAFAKI = Subintimal antegrade flossing using antegrade and retrograde intervention, TAMI = Tibio-pedal arterial minimally invasive retrograde revascularization

risk factors; however, it can also favorably affect limb-related outcomes by achieving pain relief, ulcer care or infection control, and achieving ambulation. Hence, our prime focus should be on the use of optimal medical therapy as it has been shown that optimal medical therapy is not always used. A study evaluating patients requiring infra-inguinal bypass for limb salvage had shown that nearly two-third of patients (aspirin in 50%; thienopyridine in 17%) were taking an antiplatelet drug, whereas only nearly less than half were taking lipid-lowering therapy (46%) or beta-blocker (49%).^[28] In another trial, 80% of CLI patients received an antiplatelet agent with only 46% received statin and 77% received beta-blocker.[29] Regardless of the treatment strategy employed for these patients, treating physicians must increase their efforts to place them on appropriate cardio-protective medications.

Smoking cessation, control of hypertension, and hypercholesterolemia with strict glycemic control must be ensured in these patients to achieve optimal cardio-protection. Smoking cessation has been given a high level of recommendation in various guidelines for PAD management as it has been shown to considerably decrease the progression to CLI, amputation, and mortality in these patients.^[30] Moreover, active smoking is associated with devastating cardiovascular complications including death. Adequate control of blood pressure (less than 130/80 mmHg) should be maintained in these patients, as 10 mmHg reduction in systolic blood pressure has been shown to be associated with 16% reduction in limb amputation and PAD-related deaths. Angiotensin-converting enzyme inhibitors or β -blocker therapy has been used with encouraging results (ramipril use associated with 27% decrease in the rate of combined cardiovascular events) in such patients.^[31]

Hypercholesterolemia has also been shown to be an independent predictor for the development of PAD, and lipid lowering drugs, particularly statins, have been used with a favorable reduction in cardiovascular events, mortality, and limb events following revascularization. Moreover, recent recommendations now stress the use of moderate- to high-intensity statin therapy in these patients.^[32] Moreover, patients with symptomatic PAD should also be prescribed antiplatelet monotherapy (aspirin or clopidogrel associated with a reduction in cardiovascular events in nearly a quarter of patients) as dual therapy has shown only a marginal benefit in these patients as compared to the increased risk of bleeding.^[33] Use of vasodilators such as iloprost (prostanoids) or naftidrofuryl has also been tried but with variable results.^[34] Cilastazol (phosphodiesterase III inhibitor having antiplatelet, vasodilator, and antimitogenic properties) has been shown to favorably increase skin perfusion pressure and wound healing in patients with CLI.^[35] Use of oral cilostazol (dosage of 100 mg twice daily), in addition to best medical therapy has resulted in improvement in nearly a quarter of patients with nonreconstructable CLI; however, further studies are required to adequately evaluate its role in these patients.

Revascularization

Revascularization aiming at re-establishing continuous, in-line pulsatile flow to the pedal arch remains the preferred treatment option for CLI patients, which can be achieved by surgery (lower extremity bypass or endarterectomy) or endovascular therapy. Goal of revascularization includes wound healing or treatment of at least one level of obstructive disease in case of tissue loss or ischemic pain, respectively, thereby preserving a functional limb, achieving ambulation, and preventing major limb amputation. The choice of treatment between surgical versus endovascular treatment will largely depend on various patient and procedure-specific factors such as age and co-morbidity, severity of limb ischemia, vascular anatomy/extent of involvement and presence of useable vein graft, and it should be individualized. However, in the recent years, a trend in favor of initial endovascular treatment has been seen. Although there is still a considerable amount of skepticism about the need for angiosome-related revascularization, the concept provides a framework for the interventionalist to plan the procedure. As CLI patients are very sick and have limited options for

limb salvage, modified access techniques such as subintimal antegrade flossing using antegrade and retrograde intervention (SAFARI), tibio-pedal arterial minimally invasive retrograde revascularization (TAMI), or pedal loop techniques may improve chances of recanalization in cases where even conventional methods fail to cross the lesion. Moreover, multiple technical advancements such as atherectomy devices, cryoplasty, drug-eluting balloons, and stents have been made with advanced delivery systems, which make endovascular treatment an attractive option.

However, reintervention rate is higher in the endovascular group to the tune of over 3 interventions for 1 surgical procedure declined, which fades the early benefit of this treatment option.[36-38] The Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial, the only randomized controlled trial directly comparing open bypass surgery with balloon angioplasty in CLI patients, has not shown any significant difference in terms of amputation-free survival at 1 and 3 year follow-up.^[39] Further, BEST-CLI, BASIL-2, and BASIL-3 trials are still underway, which may provide further direct comparisons between these treatment options. Among endovascular option, different drug-eluting stents were tried in PAD patients. Studies with sirolimus or everolimus drug-eluting stents have not shown any significant difference as compared to PTA or BMS; however, paclitaxel have shown promising results (improved event-free survival with superior primary patency, results being sustained at 2 years follow-up) in femoropopliteal lesions, as in ZILVER PTX trial, which allowed its FDA approval for use in PAD in 2012.^[40,41] However, its use in infrapopliteal disease is still limited to focal disease (mean lesion length 26.8 mm) and needs further validation in more common diffuse lesions.[42] Paclitaxel has proved to be a better agent than limus-class drugs, owing to its superior lipophilicity, which allows rapid uptake across cell membranes, thus reducing the risk of systemic absorption. Moreover, it can be applied directly to the metal, which obviates the risk of bio-incompatibilty of delivery polymers.

Amputation

Primary amputation rates have declined to nearly half in the previous decade with the increase in surgical or endovascular revascularization rates. Primary amputation is now reserved to patients with extensive tissue loss or infection, unreconstructable arterial disease, terminal illness, and nonambulatory status with flexion contractures. Efforts should be made to preserve knee joint, as below knee amputation is associated with reduced 30-day mortality (5% versus 16%) and increased long-term survival (74.5% versus 50.6%) as compared to above knee amputation.^[43,44]

Gene and Cell-based Therapies

Gene and cell-based therapies are emerging treatment modalities, which showed evidence for favorable outcome

in CLI patients, particularly in initial trials. Various gene (fibroblast growth factor, vascular endothelial growth factor, hypoxia inducible factor 1, and hepatocyte growth factor) and cell-based (bone marrow mononuclear cells, mesenchymal stem cells, and endothelial progenitor cells) therapies have been tried, with the majority of studies using intramuscular injection and intra-arterial delivery in minority of the protocols.^[45-50] Hepatocyte growth factor and mesenchymal stem cells currently seem most promising, however, needs further validation. Moreover, we should keep in mind that the large and especially randomized placebo-controlled trials failed to replicate these initial promising results, and future larger trials are needed to establish the efficacy of these therapies.

Platelet Rich Plasma

Use of platelet-rich plasma has also been shown beneficial for limb salvage with improvement in ulcer healing rates in CLI patients.^[51,52] Concentration and sequestration of platelets within the plasma fraction of autologous blood provide a milieu of various growth factors such as chemokines and cytokines. They may play a major role in initiation and promotion of the process of bone and soft tissue healing by enhancing *in vivo* angiogenesis, improving microcirculation, tissue remodeling, and enhanced wound healing. The notion that platelet-rich plasma could be a source of various essential growth factors, thereby directly benefiting these patients show promise, however, needs further supportive evidence by future studies.

Arterialization of Deep Veins

Deep venous arterialization (DVA) has also been shown to be a safe and feasible novel alternative to prevent major amputation in no-option CLI patients.^[53,54] It acts by providing arterialized blood at significant pressure and volumes to the ischemic tissue, thereby enabling wound healing. The LimFlow device (LimFlow SA) is currently the only registered device for total percutaneous DVA, which allows for disruption of the veins with a dedicated valvulotome, in addition to percutaneous creation of an arteriovenous fistula. Although early experience with DVA shows promising results, additional research is necessary for a better understanding of the involved physiologic mechanisms in tissue perfusion, thereby improving clinical outcomes in this subset of patients.

Future Directions

Technical advancements and ongoing research hold promise for further improvements in the management strategies of CLI patients. Combined gene and stem cell therapy may improve outcomes by selectively promoting particular cellular processes to induce a desired biological response. Moreover, it may overcome many limitations by controlling cell behavior at the intracellular signaling level. Further, ongoing research for the feasibility and efficacy of stem cell or growth factor eluting stents, bilayered stents (paclitaxel on inner layer and growth factor plasmid on outer layer), and advancements in angioplasty balloons (cryoplasty, laser, or vibrational angioplasty) may help in improving the outcome in these patients.

Conclusion

CLI poses considerable effect on the quality of patient life with huge economical impact. Moreover, the management of these patients is quite variable and not yet standardized. Revascularization remains the cornerstone of management; however, optimal revascularization strategy remains elusive. Use of optimal medical therapy should be stressed in all such patients as it is associated with improved outcome with reduction in mortality and morbidity. Recent therapeutic advances with evolving endovascular techniques and gene or cell-based therapies have the potential to dramatically change the therapeutic outlook in these patients.

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Conflicts of interest

There are no conflicts of interest.

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