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Chronic Limb-Threatening Ischemia: Current Perspective

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Editorial

Chronic limb-threatening ischemia (CLTI) is associated with high mortality, amputation, and impaired quality of life. As clinical syndrome defined by the presence of peripheral artery disease (PAD) in combination with ischemic rest pain, gangrene, or a lower limb ulceration more than 2 weeks of duration [1]. CLTI represents the end stage of peripheral artery disease (PAD), a problem of growing prevalence and increased health care costs around [2]. CLTI is a highly morbid disease, incurring significant mortality, limb loss, pain, and diminished health-related quality of life (HRQL) among those afflicted. Multiple health care specialists are involved in the management of CLTI, yet lack of public awareness and the frequent failure to make an early diagnosis continue to be major obstacles to effective treatment [3].

Usually, the impairment of peripheral perfusion is a long chronic process that occurs along months or years in relation to age, predisposing factors and cardiovascular risk factors such as smoke, diabetes, hypertension, dyslipidemia, chronic kidney disease, hypercoagulable states and hyperhomocysteinemia [4]. The diagnosis of CLTI is defined by clinical findings associated with objective peripheral examination such as ankle-brachial index (ABI), toe systolic pressure and transcutaneous oxygen pressure (TcPO₂). CLTI is considered in case of ischemic rest pain with ankle pressure <50 mmHg or a toe pressure <30

mmHg and in patients affected by foot ulcers or gangrene by an ankle pressure <70 mmHg, a toe systolic pressure <50 mmHg or TcPO₂<30 mmHg [5].

Accurately staging the severity of limb threatening is fundamental, and the Society for Vascular Surgery Threatened Limb Classification system, based on grading of Wounds, Ischemia, and foot Infection (WIFI) is endorsed. Basic Hemodynamic evaluation as well as pressure measurement such as ankle brachial index and toe pressure index should be performed for CLTI assessment requirement. Three variable independent for Evidence-based revascularization (EBR) consist of Patient risk, Limb severity, and Anatomic complexity (PLAN). Two years survival all-cause mortality were evaluated by the average-risk and high-risk patients. The Global Vascular Guideline proposes a new Global Anatomic Staging System (GLASS), which involves defining a preferred target artery path (TAP) and then estimating limb-based patency (LBP), resulting in three stages of complexity for intervention. The optimal revascularization strategy is also influenced by the availability of autogenous vein for open bypass surgery [1].

The risk of amputation is high in CLTI patients, even in those undergoing a successful revascularization [6]. CLTI is usually the result of multilevel arterial occlusive disease. Involvement of parallel vascular beds, such as the superficial femoral artery (SFA) and profunda femoral artery (PFA), is also common. Below-knee arteries typically become increasingly involved as the overall severity of disease worsens. The general requirement is that there needs to be two levels of arterial occlusive disease to cause CLTI [7]. All patients with suspected CLTI should undergo a complete physical examination [8,9]. Many patients with CLTI, especially those with DM, have “glove and stocking” sensory, motor, and autonomic neuropathy that may be asymptomatic or be associated with tingling, numbness, weakness, and burning pain in the feet and ankles [10].

In 1987, Taylor and Palmer [11] described the angiosome concept by delineating the human body into 3-dimensional blocks of tissue fed by specific arterial and venous sources, named angiosomes, that connected by collateral vessels who responsible for indirect flow supply to a vascular territory in the absence of direct flow. The infrapopliteal territory is supplied by 3 main arteries: the anterior tibial, posterior tibial, and the peroneal. Collectively, these 3 vessels supply 6 angiosomes [12]. CLTI is a complex disease process that requires a multidisciplinary team approach. This approach fosters a broader understanding of the disease with a more comprehensive use of medical, endovascular, and surgical options, and it favours collaboration over competition. Physicians possess varying degrees of skills and experience, but the goal of the team approach is to provide advanced therapies specifically for wound care and revascularization. A team approach also includes wound nurses, home health, and other resources to enhance care. When advanced therapies are not available, referral to a centre of excellence may then be appropriate. However, public reporting for lower extremity vascular procedures are not currently available, nor are there any guidelines to define operator or institutional experience related to CLTI [12].

The goal of CLTI treatment is to relieve pain, allow wound healing, improve patient’s function, prevent limb amputation and reduce mortality. Lower limb revascularization is the first-line treatment in CLTI patients that can tolerate this procedure. In few cases, CLTI patients with multiple comorbidities or low

chance of successful revascularization may require a primary amputation. A simultaneous medical intervention is required for pain management, control of cardiovascular risk factors and optimization of glycemic control [13]. Revascularization options for patients with CLTI include endovascular, surgical, or the combination of both (hybrid procedure) [12]. There is still open debate that continues today, which one is the best between open surgery rather than angioplasty. Nowadays, the decision is related to many factors such as anatomical lesions, distribution of arterial disease, patient's health status, and comorbidities, presence of foot ulcer and foot infection and local expertise [14].

Percutaneous Transluminal Angioplasty (PTA) has shown good results in term of limb salvage, feasibility and complications [14], especially for infrainguinal lesions. Open bypass surgery was known have a long term patency, endovascular procedure such as angioplasty can be performed in patients who is not suitable for open bypass due to the presence of several comorbidities and diminished life expectancy, unavailability of veins, absence of landing zone for distal bypass and foot infection in the site of potential anastomosis [15]. Angioplasty does not require general anaesthesia and usually shows few contraindications in patients with active comorbidities. Furthermore, in fragile patients with impaired renal function and in case of complex procedure, angioplasty can be performed in various steps to reduce physical stress and the amount of contrast medium administered.

The choice of revascularization technique should be examined case by case according to vascular disease and local expertise. For those who are not suitable for open bypass and endovascular therapy, currently, the new goal is to increase the local angiogenesis. Gene therapy offers a potential efficacious therapy with an acceptable rate of adverse events as documented in Phases I and II of different clinical trials [16]. Various types of gene therapies have been studied (i.e. fibroblast growth factor 1, vascular endothelial growth factor (VEGF) and hepatocyte growth factor), of which the latter currently seems the most promising [17]. Meta-analysis of randomized trials of gene therapy on VEGFs did not show significant differences between active group and placebo [18]. Otherwise, cell therapy seems to be effective in the treatment of CLTI and reduction in major amputation is documented in diabetic and non-diabetic patient [18]. Endothelial progenitor cells (EPCs) derived from bone marrow or peripheral blood are new emerging therapies to treat CLTI in this subset of patients, promoting the regeneration of impaired endothelium and neo-angiogenesis in ischemic tissues [19].

Although both gene and cell-based therapies in CLTI seem to be encouraging in the potential treatment in a subset of patients, all of these studies need more double-blinded control studies and the evaluation of longer outcomes in terms of wound healing, amputation, safety and quality of life to reinforce the initial promising results of these novel therapies.

Summary

There is renewed excitement among physicians, industry, government, and institutions in engaging the most advanced form of PAD (i.e. CLTI). Despite these efforts, many patients undergo an amputation without even a vascular assessment. Many ongoing initiatives, including the National Institutes of Health-sponsored BEST-CLI and the European BASIL II and BASIL III trials, will provide much needed

guidance regarding appropriate treatment and follow-up for patients with CLTI and help to address unanswered questions related to defining high-quality, cost-effective outcomes for this condition. At the present time, all patients who are candidates for revascularization and who present with rest pain, tissue loss, or gangrene should undergo hemodynamic assessment followed by revascularization. If local wound care or revascularization expertise is not available, or is unable to address the underlying vascular disease, patients should then be referred to specialized centres.

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