Critical limb ischaemia

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Summary
Critical limb ischaemia (CLI) is a manifestation of peripheral arterial disease (PAD) that describes patients with chronic ischaemic rest pain, or patients with ischaemic skin lesions, either ulcers or gangrene. The common meaning of the various stages of critical limb ischaemia is as follows:

- stage 1: symptomless
- stage 2: intermittent claudication
- stage 3: typical chronic ischaemic rest pain
- stage 4: ulceration or gangrene

The corresponding categories in the Rutherford classification are

- category 4 for ischaemic rest pain
- category 5 for minor tissue loss and
- category 6 for ulceration or gangrene.

Critical limb ischaemia (CLI) is a manifestation of PAD that describes patients with chronic ischaemic rest pain, or patients with ischaemic skin lesions, either ulcers or gangrene. The term CLI should only be used in relation to patients with chronic ischaemic disease, defined as the presence of symptoms for more than two weeks (35). A strict definition of chronic CLI is desirable for practical and scientific reasons.

The diagnosis of CLI should be confirmed by haemodynamic parameters such as the ankle- or toe systolic pressure or transcutaneous oxygen tension. ischaemic rest pain most commonly occurs below an ankle pressure of 50 mmHg or a toe pressure less than 30 mmHg. The ankle pressure of 50 mmHg is recommended because this includes the majority of patients for whom rest pain or ulcers do not improve spontaneously without intervention. However, since healing requires additional perfusion above that required for supporting intact skin, the ankle and toe pressure levels needed for healing are higher than the pressures found in ischaemic rest pain. For patients with ulcers or gangrene, the presence of CLI is suggested by an ankle pressure less than 70 mmHg or a toe systolic pressure less than 50 mmHg. Unfortunately, there is not complete consensus regarding the vascular hemodynamic parameters required to make the diagnosis of CLI.

Concerning clinical classification, the Fontaine classification has a long tradition and turned out as useful for many clinicians. The common meaning of the various stages involving severe ischaemia is as follows:

- stage 3, rest pain caused by arterial disease;
- stage 4, ulceration and/or gangrene caused by arterial disease.

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Peripheral arterial disease (PAD) is a serious medical problem and an indicator of systemic atherosclerosis. Concerning development and manifestation of PAD, atherosclerosis and in further consequence atherothrombosis are the main aetiopathogenic factors. In a more favorable course atherosclerosis remains clinically silent. Otherwise, by development of a progressive stenosis, patients present with claudication or in case of multisegmental disease with critical limb ischemia.

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Epidemiology and prognosis

There is little direct information on the prevalence or incidence of CLI using the mentioned definition. The overall prevalence of symptomatic PAD in patients aged between 55 and 74 years is about 3 to 4%, and the prevalence of an asymptomatic stage is about 3 to 4 times higher. Progression of intermittent claudication to rest pain or gangrene occurs in about 15–20% of patients (24).

The estimated annual incidence of CLI in Europe and USA ranges between 500 and 1000 new cases per million. In a recent study from Norway, the age-adjusted prevalence of CLI was 0.26% among men and 0.24% among women, and there was no gender difference in any age group (18). The presence of increased age, diabetes mellitus, angina pectoris, high triglyceride levels, and high body mass index were all independently associated with higher prevalence of CLI. Diabetes mellitus showed the strongest association with the prevalence of CLI among the investigated risk factors.

Patients with CLI have a high mortality because atherosclerotic disease is principally a systemic disease not localized to an isolated vessel segment. This is the reason for the high coincidence of PAD with manifestations of atherothrombosis in other vessel areas (24). Concerning cardiovascular comorbidity, the reported prevalence depends on the severity of PAD and on the sensitivity of the used diagnostic method. By coronary angiography, coronary heart disease can be observed in about 90% of patients with severe PAD. The prevalence of cerebrovascular disease is somewhat lower, and a hemodynamically significant carotid artery stenosis is found in about 15% of these patients. The diagnosis of PAD and especially also CLI is therefore a marker for mostly generalized and severe atherosclerosis, and due to this generalized atherosclerosis the prognosis of patients with PAD is poor concerning overall survival. Patients with CLI have an even worse prognosis compared to patients presenting with claudication. It has been demonstrated that there is an almost linear relationship between ankle-brachial-index (ABI) and the risk of fatal and non-fatal cardiovascular events. Each decrease in ABI of 0.10 is associated with a 10% increase in relative risk for a major vascular event (24). Observational studies of patients with CLI who are not candidates for revascularization suggest that one year after the onset of CLI, only about half the patients will be alive without a major amputation, approximately 25% will have died and 25% will have required a major amputation (24).

The diagnosis of CLI thus predicts a poor prognosis for life and limb. Cardiovascular diseases, especially myocardial infarction and stroke, are the usual cause of death in these patients. Their prognosis after amputation is even worse. The perioperative mortality for below-knee amputation in most series is 5–10% and for above-knee amputation 15–20%. Furthermore, one-third of amputated patients die within 1 year, one-third achieve partial autonomy and only one-third obtain complete autonomy (11).

Pathophysiology and risk factors

CLI occurs when arterial lesions impair blood flow and distal perfusion pressure to a level insufficient to satisfy the nutritive needs of the limb at rest despite compensatory mechanisms such as collateral formation. This usually results from the presence of multilevel occlusive disease or occlusion of critical collaterals. The ultimate cause of CLI is then maldistribution of skin microcirculation in addition to reduced total blood flow. The importance of the microcirculation in CLI is suggested by a wide overlap in ankle or toe blood pressure in patients with PAD and with or without CLI. Capillary microscopy in CLI has shown initial tissue edema and pericapillary hemorrhage followed by a reduction in the number of perfused capillaries. The net result in ischaemic areas is an inhomogeneous perfusion of the skin microvessels (35). Atherosclerosis is the fundamental process in the pathogenesis of CLI. Occasionally, inflammatory arteritis (e. g. thromboangiitis obliterans) can cause CLI.

Our understanding about pathogenesis of atherosclerosis has changed fundamentally during the last decades. While atherosclerosis was formerly considered a bland lipid storage disease, substantial advances in basic and clinical studies have illuminated the role of inflammation and the underlying cellular and molecular mechanisms that contribute to atherogenesis (19,29). It can be considered to be a form of chronic inflammation. The extent of inflammation as measured by specific biomarkers likely reflects the activity of the disease and thus may predict the individual’s risk for progression of atherosclerosis. In this context, numerous studies elucidated the association between inflammation and clinical surrogate markers of atherosclerosis progression. Among the panel of potentially useful parameters high sensitivity C-reactive protein (hs-CRP) has been unequivocally demonstrated to predict – with a predictive value exceeding that of LDL cholesterol – disease progression and clinical adverse events (27,32). The interplay between inflammatory and hemostatic mechanisms may also play a crucial role in the development and progression of atherosclerosis/atherothrombosis (22).

Genetic factors are responsible for a basic risk of a patient for development of atherosclerotic disease, and this basic risk is modified under the influence of further modifiable personal and environmental factors. Many reports have found a significant difference in the risk of PAD by ethnic group, with some of the risk difference attributed to different levels of traditional cardiovascular risk factors. However, such ethnic associations with PAD remain significant even after adjustment for traditional and novel risk factors (3). Understanding the inherited factors that may influence patients’ susceptibility for suffering future atherothrombotic events could lead to the development of better and more comprehensive therapies.

The major established risk factors for PAD include smoking, hyperlipidemia, hypertension and – especially for development of CLI – presence of diabetes. Diabetic patients are at least fivefold more likely to develop CLI than nondiabetic patients. During a 5-year period in the Basle study, 6.8% of
diabetic patients with symptomatic or asymptomatic PAD required amputation compared with 0.6% for patients without overt diabetes (35).

Diagnosis

Symptoms and signs

A careful history taking and clinical examination remain the golden standard in diagnosis of PAD including CLI. Patients with CLI usually present with limb pain at rest, with or without trophic skin changes or tissue loss. Ischaemic rest pain most typically occurs at night - when the limb is no longer in a dependent position - but in severe cases can be continuous. The pain is localized in the distal part of the foot or in the vicinity of an ischaemic ulcer or gangrenous toe. The pain often wakes the patients at night and forces them to get up, or take a short walk around the room. Partial relief may be obtained by the dependent position, whereas elevation and cold increase the severity of the pain. Patients often sleep with their ischaemic leg dangling over the side of the bed, or sitting in an armchair, and as a consequence ankle and foot edema develop. Ischaemic rest pain has to be differentiated especially from neuropathic pain.

The clinical examination demonstrates - besides absent peripheral pulses - often changes in skin color and temperature. Specific findings may include hair loss, muscle atrophy, atrophy of subcutaneous tissues and skin, dry fissured skin, discoloration and petechial bleedings (Fig. 1a).

Sometimes it is clinically difficult to evaluate the diagnostic and prognostic importance of tissue defects. A distinction must be made between skin damage associated with PAD and that caused by PAD due to CLI. Patients with PAD and claudication may have tissue defects as a result of trauma - mostly minor injuries - that is not indicative of CLI but rather of complicated stage II of PAD. Some patients may progress through rest pain into tissue loss. However, in many patients, notably those with diabetic neuropathy, the initial presentation is with a neuroischaemic ulcer or gangrene (Fig. 1b).

Apparative diagnosis

Measurement of the ankle pressure and calculation of the ankle-brachial index is worldwide established as the initial functional test. In patients with ischaemic ulcers the ankle pressure is typically 50–70 mmHg, and in patients with ischaemic rest pain it is typically 30–50 mmHg.

In case of mediasclerosis – mainly in diabetics – the measurement of ankle pressure is replaced by toe pressures with a critical level < 30 mmHg. Investigation of microcirculation is helpful, but primarily used as a research tool. Measurement of the transcutaneous pO₂ is a widely accepted method to assess the microcirculatory perfusion.

Morphologic evaluation is obligatory in all patients with CLI, since any kind of revascularization should be done whenever technically possible. This can be done by duplexsonography, computed tomographic angiography (CTA) or magnetic resonance angiography (MRA), while intraarterial digital subtraction angiography as the former gold standard should not be used for only diagnostic purpose anymore. This invasive investigation should only be done immediately before an endovascular intervention during the same procedure.

Duplexsonography as the primary diagnostic step for evaluation of morphology and for planning the kind of revascularization – endovascular or surgical technique – enables visualization and quantification of severity of lesions. The main disadvantages are its operator-dependency, the limited field of view and the limited imaging in patients with severe calcification such as in diabetics. Therefore, this method has limitations especially in patients with CLI. Due to rapidly improving technology, both CTA and MRA have become more established and are now more widely used during the last years for initial imaging in patients with PAD. Both produce images of vascular structures in cross-sectional slices that can be reformatted into three-dimensional angiographic images. In a randomized trial comparing MRA with CTA for initial imaging in PAD, the two techniques were similar in ease of use and clinical outcome (25). It mainly depends on the local availability and expertise which method is preferentially used. The main disadvantages of CTA are the time-consuming postprocessing, the ionizing radiation and the use of iodinated contrast material. Therefore until recently MRA was primarily recommended in patients with impaired kidney function. However, recently the first observations were reported which indicated that exposure to gadolinium-containing contrast agents during MRA in patients with advanced renal disease (estimated glomerular filtration rate < 60 ml/min/1.73 m²) may cause a severe skin disease called nephrogenic fibrosing dermopathy (NFD) characterized by thickening and hardening of the skin, mostly in the extremities (30). These skin lesions can progress rapidly, sometimes leading to joint immobility and the inability to walk. Clinicians should be aware of the potential for NFD, and when possible, should avoid use of gadolinium-containing contrast agents in patients with advanced renal disease.
Treatment

The primary goals of the treatment of CLI are to relieve ischaemic pain, heal (neuro)ischaemic ulcers, prevent limb loss, improve patient function and quality of life and prolong overall survival. In order to achieve these outcomes, most patients will ultimately need a revascularization procedure requiring referral to a vascular center. Therefore it is definitely recommended in the TASC paper (24) that “Patients with CLI should be referred to a vascular specialist early in the course of their disease to plan for revascularization options”. In contrast to CLI, most patients with intermittent claudication can primarily be treated conservatively, since intermittent claudication can be considered a lifestyle limiting condition rather than an immediate threat to limbs. Furthermore, in patients with CLI a multidisciplinary approach is recommended to control pain, cardiovascular risk factors and other co-morbid diseases and for treatment of critical limb ischaemia.

Risk factor control

Cardiovascular risk factor control is mandatory in CLI patients as well as in all PAD patients. The REACH registry has clearly demonstrated that despite their well-known adverse effects, the classic cardiovascular risk factors are still largely undertreated and undercontrolled in many regions of the world (6). The first priority in treatment of patients with PAD is to try to adjust the known vascular risk factors to decrease the progression of atherosclerosis and to prevent the development of atherothrombotic complications.

Smoking

The importance of smoking cessation is well established and special emphasis should be given to this point during each visit of a patient with PAD and especially with CLI. Patients should be encouraged to stop smoking primarily to reduce their risk of cardiovascular events, as well as their risk of progression of disease to amputation. In the recent TASC paper it is a grade A recommendation that all patients who smoke should receive a program of physician advice, group counseling sessions, and nicotine replacement (24).

Lipids

Concerning the general cardiovascular risk, the presence of PAD is considered as coronary heart disease risk equivalent. Therefore dietary modification and pharmacologic therapy with regard to dyslipidaemia should be tailored to meet the current guidelines for high risk patients. Concerning low-density lipoprotein cholesterol, a value of less than 100 mg/dl or even less than 70 mg/dl for those at very high risk should be the goal (15). HMGCo-A reductase inhibitor drugs (statins) exert several beneficial properties in atherosclerotic disease and have been demonstrated unequivocally to reduce cardiovascular events and mortality in cardiovascular high risk patients (16). Statins may prevent plaque instability and thrombosis due to their pleiotropic effects, as improvement of endothelial function, reduction of inflammation, and stabilization of atherosclerotic plaques. Statin therapy was especially associated with improved survival and event-free survival rates in patients with severe PAD in states of high inflammatory activity (33). Statins, therefore, should be rigorously prescribed in these patients.

Hypertension

The importance of intensive blood pressure control for reduction of cardiovascular events has especially been demonstrated in PAD patients with diabetes (23). Beta-adrenergic blockers have until recently been considered relatively contraindicated in these patients because of the perceived risk that these drugs could reduce the peripheral circulation by inhibition of beta-2-receptors and thus worsen intermittent claudication. However, beta-blockers are definitely not contraindicated in patients with intermittent claudication (26). On the contrary, due to their cardioprotective effect they are associated with improved survival in patients with PAD (14). Otherwise, these drugs should be prescribed cautiously in patients with CLI.

In the Heart Outcomes Prevention Evaluation study – including also patients with PAD –, the risk of heart attack, stroke, and death from vascular causes was reduced by 22% for patients given the angiotensin-converting enzyme inhibitor ramipril (43). This effect was independent of its antihypertensive effect.

Diabetes mellitus

Diabetes mellitus is highly associated with PAD and its progression and especially with development of CLI. Rigorous control of blood glucose prevents the micro-vascular complications of diabetes, although similar benefits on the macro-circulation have not been ascertained (38). Patients with diabetes and PAD should have an aggressive control of blood glucose levels with a hemoglobin A1c goal of < 7.0% or as close to 6% as possible. In the new TASC paper this recommendation is graded as C, meaning that it is based on evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities, while there are no applicable studies of good quality (24). Such intensive therapy, achieving a Hba1c of below 7%, elicited a trend for reduced risk of non-fatal cardiovascular events by 41% (from 0.8 to 0.5 events per 100 patients –years), but had no effect on the risk of death or amputation. Furthermore, each 1% increase in Hba1c was associated with a 28% increase in risk of incident PAD (2).

Secondary prophylaxis

The main reason to administer antiplatelet therapy to patients with PAD is to prevent severe vascular events such as myocardial infarction, stroke or vascular death. The Antiplatelet Trialists’ Collaboration metaanalysis found that among 9214 patients with PAD in 42 trials, there was a 23% reduction in serious vascular events (p = 0.004) in patients treated with antiplatelet therapy (4). The CAPRIE trial (Clopidogrel versus Aspirin in Patients at Risk of ischaemic Events) demonstrated that the combined risk of death from vascular causes, myocardial infarction, and stroke...
was significantly, albeit moderately, lower with clopidogrel (75 mg/day) compared with aspirin (325 mg once daily) (8). Despite this difference, in the 8th ACCP Conference on Antithrombotic and Thrombolytic Therapy – published in 2008 – it was recommended – by placing a relatively high value on avoiding large expenditures to achieve small reductions in vascular events – to use aspirin rather than clopidogrel in PAD patients without clinically manifest coronary or cerebrovascular disease (36). Unfortunately, the recent TASC II paper does not give clear recommendations concerning this point.

During the last years, „resistance“ to antiplatelet drugs has become a major point of interest. Inter-patient variability in drug response has been shown to be – at least partially – the result of polymorphisms in genes encoding drug targets, such as receptors or enzymes (41). Many tests of platelet function are now available for clinical use, and some of these tests have shown that hypersensitivity to antiplatelet drugs in the laboratory (i.e. resistance) is associated with adverse clinical events in different patient populations (13). However, in most of these studies, the number of major adverse clinical events was low. Furthermore, uniform definitions and standardized assays are not yet available, and there are also no published studies addressing the clinical effectiveness of altering therapy based on the results of monitoring antiplatelet therapy. Therefore monitoring of antiplatelet therapy in patients with vascular disease currently cannot be generally recommended for clinical routine.

Revascularization

Revascularization is the therapy of choice in patients with CLI (24). The optimal strategy for management of a patient with CLI must be determined on a case-by-case basis. Important issues to consider include the urgency of the clinical presentation, the presence of comorbidity, and the arterial anatomy. A significant improvement in inflow may diminish the symptoms of rest pain, but pulsatile flow to the foot is generally necessary for the treatment of ischaemic ulcers or ischaemic gangrene.

From a clinical point of view, one major shortcoming of the TASC II document in the context of revascularization is that the underlying indication for treatment, whether it is intermittent claudication or CLI, is not considered and hardly discussed as a relevant factor. The clinical indication for revascularization should be the most important determinant for our medical decision making. In patients with intermittent claudication, mid- and long-term results count, particularly in the femoropopliteal segment where surgery remains superior with respect to long-term durability. In contrast, in CLI patients the acute and short-term results (at the treated artery) are of major importance to resolve critical ischaemia and allow ulcer healing. Undoubtedly, endovascular therapy seems equivalent to surgery in this context. Endovascular therapy emerged as one of the most rapidly evolving fields in medicine during the last decade (28), and due to the advances in techniques and technology, endovascular approaches now represent the initial strategy for management of most of these mostly polymorbid and therefore high-risk patients. The main advantages of endovascular revascularization are a low complication rate ranging between 0.5% and 4%, a high technical success rate even in long occlusions approaching 90%, and an acceptable short-term clinical outcome. In accordance with vascular surgery, unique reporting standards are required to obtain comparability of studies dealing with endovascular therapy of peripheral arteries to further elucidate and to prove long-term credibility of this method (10). Bypass surgery with venous grafts must still be considered the most durable revascularization technique for patients with chronic limb ischaemia and extensive disease in the superficial femoral artery (24), although the recently reported Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial demonstrated that rates of amputation-free survival are similar for surgery and balloon angioplasty for at least the first 2 years after the procedure (1). Endovascular stents in the femoropopliteal segment resolved the problems of early elastic recoil, residual stenosis and flow-limiting dissections after PTA and enabled treatment of long and complex lesions even in heavily calcified arteries. Especially in patients with CLI – suffering mostly from complex and long lesions – it is of great importance to achieve an optimal primary result (Fig. 2a). Most interventionists know that such an optimal result can be achieved very often only by an additional stent implantation. Looking at the recent studies, it became clear that the introduction of nitinol stent technology has definitely improved the results of stenting in the superficial femoral artery and has broadened the indication for stenting (34). Therefore, nitinol stents currently seem to be an effective alternative to surgical revascularization of longer lesions in poor surgical candidates with severe cardiovascular comorbidity. Furthermore, stenting may be an option for patients without available saphenous vein

Vasoactive drugs

In patients with CLI not eligible for arterial reconstruction, prostanoids are the only vasoactive drugs with proven efficacy. The currently available data support the use of prostanoids in patients who are unsuitable for any procedure or in whom revascularization attempts have failed. The majority of studies have found that parenteral administration of either PGE1 or iloprost reduced pain, as assessed by analgesic consumption, ulcer size, and/or amputation. (24). Creutzig et al. (9) concluded in a recent metaanalysis of randomized placebo-controlled trials, that for patients with PAD stage III or IV PGE1 therapy not only has significant beneficial effects over placebo on ulcer healing and pain relief, but also increases the rate of patients surviving with both legs after 6-months follow-up. However, in a recent randomized, multicenter, double blind and placebo controlled trial – including 383 patients – the prostanoid lipo-ecaprost (a lipid encapsulated prostaglandin E1 prodrug) failed to reduce death and amputation during 6 months follow-up (7). Therefore there is no clear recommendation in TASC II concerning use of prostanoids in CLI. However, it is also stated that there are no other pharmacotherapies that can be recommended for the treatment of CLI.
grafts, as the 12-month stent patency data are comparable to those for prosthetic bypass grafts and stenting has a considerably lower rate of complications. However, the endovascular approach only seems justified as long as low rates of complications are encountered and the surgical landing zone for the distal anastomosis of a potential secondary bypass operation remains unaffected by the interventional procedure.

Concerning the choice between endovascular or surgical techniques with equivalent short- and long-term clinical outcomes, it is stated in the TASC paper as „Recommendation 35: In a situation where endovascular revascularization and open repair/bypass of a specific lesion causing symptoms of peripheral arterial disease give equivalent short-term and long-term symptomatic improvement, endovascular techniques should be used first“ (24).

For CLI patients, the indication for stenting has to be established quite liberally to obtain an optimal primary result and to guarantee resolution of the critical perfusion deficit. In the near future, drug-eluting stents may help to further improve the durability of stents in the lower limb arteries. As yet, trials evaluating drug-eluting stents were underpowered and showed disappointing long-term outcomes (12). Nevertheless, the concept of combining the advantages of the mechanical scaffolding properties of nitinol stents with the antiproliferative action of drugs seems appealing. Alternative promising strategies to prevent restenosis are drug-coated balloons and biodegradable stents. Stent grafts have been developed as therapy for femoropopliteal occlusive disease in an effort to duplicate the surgical gold standard of femoropopliteal bypass with either vein or synthetic graft material.

In CLI, multi-level disease is mostly seen. However, especially in diabetics, arteries proximal to the knee joint are often spared or only moderately diseased, while the majority of occlusions occur at the tibial peroneal trunk and distally (Fig. 2b). Endovascular therapy has been established also in lower leg arteries during the last years. The TASC II document reads: „There is increasing evidence to support a recommendation for angioplasty in patients with CLI and infrapopliteal artery occlusion where inline flow to the foot can be re-established and where there is medical comorbidity.“ Such medical comorbidity can be observed in most patients, as it is well documented that patients with CLI and tibioperoneal disease have a high coincidence with other atherosclerotic diseases as coronary artery disease.

The risks of surgery in these mostly high-risk patients (diabetics, renal insufficiency) have led, together with the improved technology, to a steadily increasing application of endovascular interventions also in the infrapopliteal arteries. However, treatment of CLI is the only generally accepted indication for below-knee endovascular interventions, while isolated infrapopliteal endovascular intervention is rarely indicated in patients with intermittent claudication. An additional important indication for below-knee angioplasty is to improve run-off and subsequent long-term patency after femoropopliteal angioplasty/stenting or bypass grafting. Until recently, stenting of the crural vessels was recommended only in case of complication. However, recently studies have also been published concerning stent implantation for the treatment of focal infrapopliteal lesions to improve long-term patency (31).
Therapeutic angiogenesis for CLI (39)

Soon after the identification of angiogenic growth factors, cardiovascular investigators began testing the hypothesis that stimulating angiogenesis could improve perfusion and function in ischaemic tissues independent of macrovessel manipulation. Abundant preclinical data supported the safety and clinical potential of therapeutic angiogenesis that used growth factors or cellular-based strategies. Members of the vascular endothelial growth factor (VEGF) family are among the most powerful modulators of vascular biology. They regulate vasculogenesis, angiogenesis, and vascular maintenance during embryogenesis and in adults (42). Because of their profound effects on blood vessels, VEGFs have received much attention regarding their potential therapeutic use in cardiovascular medicine, especially for therapeutic vascular growth in myocardial and peripheral ischaemia. However, completed randomized controlled VEGF trials have not provided convincing evidence of clinical efficacy. Emerging evidence supports a role of bone marrow-derived, circulating endothelial progenitor cells (17). These cells originate from the bone marrow, circulate in the peripheral blood, and play a crucial role in the repair or formation of blood vessels. They contribute to the maintenance of endothelial function and organ perfusion by mechanisms ranging from endothelial repair to postnatal angiogenesis and vasculogenesis (5). In vivo, therapeutic angiogenesis and vasculogenesis using autologous transplantation of nonnuclear bone marrow cells or ex vivo expanded endothelial progenitor cells improved tissue injury and organ function following ischaemia of a limb (37) or of the heart in humans. However, considering the relatively few number of patients treated by angiogenic therapy, the interpretation of clinical results has to be done with caution.

Furthermore, a number of concerns need to be addressed, including the potential for angiogenesis-triggered malignancies, the impact of angiogenesis on physiological or pathological processes, and the specific adverse effects associated with each growth factor. There is also concern that angiogenic factors may promote or destabilize atherosclerotic plaques by exerting angiogenic effects on the vasa vasorum. Nevertheless, clinical studies have found no evidence of accelerated atherosclerosis in patients with advanced vascular/arteriosclerotic disease who were administered angiogenic cytokine therapy (20, 21). Summarizing this promising treatment modality for patients with CLI, we still have to prove safety and efficacy of the various forms of therapeutic angiogenesis before one can conclude on its role as an additional limb saving strategy. It is still a long way from bench to bedside and patient benefit, despite a considerable number of ongoing clinical trials.

Independent of the technical approach—whether it may be gene-therapy, application of angiogenic growth factors or cytokines, stem-cell therapy by transplantation or mobilization—therapeutic angiogenesis should be considered only when all endovascular interventional and surgical options for perfusion improvement failed.

Spinal cord stimulation

There are several theories attempting to explain the mechanisms of action of spinal cord stimulation (SCS), but they are not yet completely understood. SCS at lumbar spinal segments (L2-L3) produces vasodilation in the lower limbs and feet which is mediated by antidromic activation of sensory fibers and decreased sympathetic outflow. A recent meta-analysis about SCS showed that the additional use of SCS to the standard conservative treatment is better than the standard conservative treatment alone (40). Pooled data showed a significant beneficial effect in terms of limb salvage with a relative risk of 0.71 (95% CI: 0.56–0.90) after 12 months of treatment in patients without any option to vascular reconstruction. In addition, there is some evidence of ulcer healing and pain relief with spinal cord stimulation.

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