Chapter I: Definitions, Epidemiology, Clinical Presentation and Prognosis

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Abstract   The concept of chronic critical limb ischaemia (CLI) emerged late in the history of peripheral arterial occlusive disease (PAOD). The historical background and changing definitions of CLI over the last decades are important to know in order to understand why epidemiologic data are so difficult to compare between articles and over time. The prevalence of CLI is probably very high and largely underestimated, and significant differences exist between population studies and clinical series. The extremely high costs associated with management of these patients make CLI a real public health issue for the future. In the era of emerging vascular surgery in the 1950s, the initial classification of PAOD by Fontaine, with stages III and IV corresponding to CLI, was based only on clinical symptoms. Later, with increasing access to non-invasive haemodynamic measurements (ankle pressure, toe pressure), the need to prove a causal relationship between PAOD and clinical findings suggestive of CLI became a real concern, and the Rutherford classification published in 1986 included objective haemodynamic criteria. The first consensus document on CLI was published in 1991 and included clinical criteria associated with ankle and toe pressure and transcutaneous oxygen pressure (TcPO$_2$) cut-off levels ($\leqslant$50 mmHg, $\leqslant$30 mmHg

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and $\leqslant$10 mmHg respectively). This rigorous definition reflects an arterial insufficiency that is so severe as to cause microcirculatory changes and compromise tissue integrity, with a high rate of major amputation and mortality. The TASC I consensus document published in 2000 used less severe pressure cut-offs (<50−70 mmHg, <30−50 mmHg and <30−50 mmHg respectively). The thresholds for toe pressure and especially $TcPO_2$ (which will be also included in TASC II consensus document) are however just below the lower limit of normality. It is therefore easy to infer that patients qualifying as CLI based on TASC criteria can suffer from far less severe disease than those qualifying as CLI in the initial 1991 consensus document. Furthermore, inclusion criteria of many recent interventional studies have even shifted further from the efforts of definition standardisation with objective criteria, by including patients as CLI based merely on Fontaine classification (stage III and IV) without haemodynamic criteria. The differences in the natural history of patients with CLI, including prognosis of the limb and the patient, are thus difficult to compare between studies in this context. Overall, CLI as defined by clinical *and* haemodynamic criteria remains a severe condition with poor prognosis, high medical costs and a major impact in terms of public health and patients' loss of functional capacity. The major progresses in best medical therapy of arterial disease and revascularisation procedures will certainly improve the outcome of CLI patients. In the future, an effort to apply a standardised definition with clinical and objective haemodynamic criteria will be needed to better demonstrate and compare the advances in management of these patients.

1. Introduction

The concept of chronic critical limb ischaemia (hereafter referred to as CLI) emerged late in the history of peripheral arterial occlusive disease (PAOD). It refers to a state of arterial insufficiency that reduces distal perfusion pressure to such an extent that microcirculation and nutrient blood flow to tissues are severely disturbed. Much of the interest in CLI originally focused on defining an accurate and objective description of patients that could allow a thorough comparison between various treatment modalities. Indeed, early in the history of CLI, a true need for greater objectivity in characterising patients undergoing surgical procedures was felt, with the aim of getting rid of subjective terms such as "limb-threatening ischaemia" and "limb salvage operations". Later, such standardisation was also judged necessary to define patients in non-surgical management trials.

This review first presents the historical background of CLI and its evolving definitions over time, as well as the available epidemiologic data. Then, the hallmarks of CLI clinical presentation are described, with an emphasis on the need for objective haemodynamic confirmation of the causal link between PAOD and clinical findings. Finally, the prognosis of CLI is discussed as well as some risk stratification tools.

2. Historical background

In 1952, during the first meeting of the European Society for Cardiovascular Surgery dedicated to aorto-iliac lesions, Fontaine et al. introduced a simple clinical classification of patients with chronic arterial disease of lower limbs (LL) in four stages.[1] At that time, vascular surgery was emerging and patients used to present with advanced disease often associated with obvious symptoms and signs of chronic severe ischaemia. Moreover, haemodynamic measurements were almost non-existent (the first demonstration of a fall in ankle pressure in PAOD was made by Windsor in 1950), so

that Fontaine's classification implied a causal link between the symptoms and signs and PAOD. Unfortunately, Fontaine's classification is nowadays too often used as "(any) rest pain + PAOD = PAOD stage III" or "(any) ulceration or gangrene + PAOD = PAOD stage IV", regardless of the actual severity of PAOD.

In 1969, Yao introduced measurement of the ankle-brachial pressure index (ABI) with a 10 MHz Doppler probe, and demonstrated a pressure drop proportional to the severity of occlusive lesions.[2] Yao also showed significant differences in ABI ranges across Fontaine stages, despite some overlap between stages II and III, and stages III and IV.[3] However, only patients with proximal (iliac or femoro-popliteal) lesions were included, thus excluding a significant number of patients with leg artery calcification. At the same period, the accuracy of toe pressure for quantification of arterial insufficiency in PAOD was demonstrated by Carter et al.[4]

The expression "critical ischaemia" appeared in 1982 in the literature to describe LL ischaemia of such severity that major amputation became necessary in the absence of successful revascularisation.[5] This definition included an absolute ankle systolic pressure <40 mmHg in case of rest pain and <60 mmHg in case of ulcer or gangrene. Nevertheless, it soon appeared that ankle pressure was inadequate in case of ulcer or gangrene, toe pressure being a better predictor of foot viability particularly in diabetic patients, and that an evaluation of skin perfusion could be useful.[6,7]

In 1986, the First Society for Vascular Surgery/ International Society for CardioVascular Surgery (SVS/ISCVS) Standards for reports dealing with lower extremity ischaemia were published,[8] including a recommendation for staging chronic limb ischaemia that would become known as the Rutherford classification. This classification is similar to Fontaine's classification, but its originality lies in adding an objective criterion to each clinical category: resting ankle pressure <40 mmHg/flat or barely pulsatile forefoot pulse volume recording/toe pressure <30 mmHg for ischaemic

rest pain (Grade II, Category 4); resting ankle pressure <60 mmHg/flat or barely pulsatile forefoot pulse volume recording/toe pressure <30 mmHg for minor (Grade III, Category 5) or major (Grade III, Category 6) tissue loss. All these criteria remained unchanged in the 1997 revised version of SVS/ISCVS Standards for reports dealing with lower extremity ischaemia.[9] Unfortunately, in the Trans-Atlantic Inter-Society Consensus (TASC) Document on Management of Peripheral Arterial Disease[10] and thereafter, only the clinical description of Rutherford categories are maintained, and Rutherford classification as often used nowadays has lost what made its strength compared to Fontaine's classification.

Of note, Fontaine and Rutherford classifications were suggested by individual physicians. The first experts' *consensus* document on CLI was published in April 1991 after the Second European Meeting on Chronic Critical Leg Ischemia,[11,12] followed by TASC I and II consensus documents.[10,13]

These different suggested definitions of CLI are discussed in detail in the following section, but this historical reminder seemed important to us. Indeed, when reading many recent articles, one can wonder if the original purpose of creating the term CLI with a rigorous and objective definition has not been somewhat forgotten.

3. Definitions of chronic critical limb ischaemia

CLI represents the end stage of PAOD, in which macrovascular lesions induce such a reduction of distal perfusion pressure that microcirculation and nutrient blood flow to the tissues are severely disturbed. It is important to emphasise that the definition of CLI has evolved over time, from the initial document of 1991 to TASC I and II consensus documents published more recently. These three definitions are presented and commented on below. The concept of chronic subcritical limb ischaemia is also briefly discussed at the end of this section.

3.1. Second European Meeting Consensus document on CLI (1991)[11]

This document includes two levels of CLI definition reproduced below as they appear in the original version: one for clinical use in daily practice, and the second for clinical research and publications.

Recommendation 1
CLI, in both diabetic and non-diabetic patients, is defined by either of the following two criteria:
• *persistently recurring ischemic rest pain requiring regular adequate analgesia for more than two weeks with an ankle systolic pressure ⩽50 mmHg and/or toe systolic pressure ⩽30 mmHg;*
• *ulceration or gangrene of the foot or toes, with an ankle systolic pressure ⩽50 mmHg or toe systolic pressure ⩽30 mmHg.*

Of note, the terms rest pain, ulceration or gangrene should be applied according to the classical description of *ischaemic* rest pain and trophic changes (see section 5 on clinical presentation of CLI).

Recommendation 2
A more precise description of the type and severity of CLI is also necessary for the design and reporting of clinical trials. In addition to the above definition (Recommendation 1), the following information is also desirable:
• *arteriography to delineate the anatomy of the large vessel disease throughout the leg and foot;*
• *toe arterial pressure in all patients, including those who are not diabetic;*
• *a technique for quantifying the local microcirculation in the ischemic area [e.g. capillary microscopy, transcutaneous oxygen pressure (TcPO2), or laser Doppler].*

Of note, $TcPO_2$ is usually ⩽10 mmHg in supine position in CLI patients and is not increased with inhalation of oxygen; further sensitivity may be obtained by performing the measurements in sitting position.

Soon after its publication, this definition was criticised, mainly because an ankle pressure threshold of 50 mmHg was judged too low. Furthermore, the true interest of ankle pressure was questioned, particularly in diabetic patients.[12,14] Nevertheless, these criteria seemed well accepted by vascular surgeons, as demonstrated by a computer-interactive voting session during the European Society for Vascular Surgery (ESVS) meeting in Barcelona in 1993. Among 158 participants, of whom 82% were vascular surgeons, 83% agreed on either ankle pressure ⩽50 mmHg (55%) or toe pressure ⩽30 mmHg (28%), and 12% preferred to add a microcirculatory parameter to define CLI.[15]

3.2. Trans-Atlantic Inter-Society Consensus (TASC) Document on Management of Peripheral Arterial Disease (2000)[10]

This document includes the following recommendations concerning CLI.

Recommendation 73 Clinical definition of critical limb ischemia (CLI)
The term critical limb ischemia should be used for all patients with chronic ischemic rest pain, ulcers, or gangrene attributable to objectively proven arterial occlusive disease. The CLI implies chronicity and is to be distinguished from acute limb ischemia.

Recommendation 74 Trials and reporting standards definition of CLI
A relatively inclusive entry criterion is favoured, the aim being to ensure that the ulceration, gangrene, or rest pain is indeed caused by peripheral arterial disease and that most would be expected to require a major amputation within the next 6 months to a year in the absence of a significant haemodynamic improvement. To achieve this, it is suggested to use absolute pressures of either ankle pressure <50–70 mmHg or toe pressure <30–50 mmHg or reduced supine forefoot TcPO2 <30–50 mmHg.

Some points need to be discussed. First, the expression "attributable to objectively proven PAOD" used in Recommendation 73 is very important. Indeed, the association of rest pain or trophic changes on the distal part of a leg with PAOD does not mean *ipso facto* that PAOD is in CLI stage, i.e. severe enough to explain the clinical symptoms and/or signs presented by the patient. Second,

raising the threshold of ankle pressure to 70 mmHg does not seem a good compromise in response to the criticisms on ankle pressure mentioned above. It might have been a better choice to favour toe pressure measurement instead for the objective confirmation of CLI in a given patient (see the recommendations in section 7). Third, the new threshold values used in this document for toe pressure are just below the ranges found in patients with intermittent claudication. For forefoot $TcPO_2$, the suggested cut-off is even at the lower limit of values found in patients without PAOD.

3.3. Trans-Atlantic Inter-Society Consensus (TASC) Document on Management of Peripheral Arterial Disease II (2007)[13]

In this document, the recommendations are presented in a summarised version.

<u>Recommendation 16</u> *Clinical definition of critical limb ischemia (CLI)*
The term critical limb ischemia should be used for all patients with chronic ischemic rest pain, ulcers or gangrene attributable to objectively proven arterial occlusive disease. The term CLI implies chronicity and is to be distinguished from acute limb ischemia.

<u>Recommendation 19</u> *Diagnosis of critical limb ischemia (CLI)*
CLI is a clinical diagnosis but should be supported by objective tests.

Details and objective criteria can only be found in the full text as follows: "Ischemic rest pain most commonly occurs below an ankle pressure of 50 mmHg or a toe pressure less than 30 mmHg. [. . .] 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. (It is important to understand that there is not complete consensus regarding the vascular haemodynamic parameters required to make the diagnosis of CLI.)"

As summary recommendations are more often read than the full text, only the items rest pain and ulcer or gangrene remain highlighted over time, and the objective criteria have lost their importance, being perceived as accessory. This trend has unfortunately led to a major backward step in the development of the concept of CLI, with a return to initial definitions of 1950s based merely on clinical findings, as in Fontaine stages III and IV. This is highly regrettable, considering all the efforts undertaken over the last two decades to standardise an objective and reproducible definition of CLI.

3.4. General comments on the haemodynamic parameters used to define CLI

After presenting the different definitions suggested for CLI, it seems important to discuss some points concerning the haemodynamic assessment methods used in these definitions.

First, it should be emphasised that ankle systolic pressure (expressed as an absolute value or as ABI) is not a highly reliable parameter in patients with suspected CLI. Although an ABI ⩽0.40 or an ankle pressure ⩽50 mmHg (measured in supine position or using the "pole test" method)[16,17] is consistent with a diagnosis of CLI, toe pressure measurement should clearly be recommended for all patients with suspected CLI.[18,19] Indeed, ankle pressure measurement is subject to erroneous results in patients with leg artery calcification, mainly represented by patients with diabetes or end-stage renal failure and in the very old, the measured value reflecting arterial wall rigidity rather than the actual perfusion pressure.[19,20] If the arteries are still partially compressible, falsely elevated (and reassuring) pressure values are measured. In case of incompressibility, no pressure result can be obtained. Lack of compressibility is exceptionally an issue when measuring toe pressure.

Then, methods providing functional information on tissue perfusion and skin viability, such as forefoot $TcPO_2$, are still too seldom used mainly because of their limited availability.[21] When performed properly, forefoot $TcPO_2$ has a high prognostic value (see section 6.2 on risk stratification). Its use on a larger scale should therefore be strongly encouraged in vascular clinics.

3.5. Chronic "subcritical" limb ischaemia

The expression "chronic subcritical limb ischaemia" was first introduced by Wolfe et al. to name a state of lower limb ischaemia borderline to CLI as defined in the 1991 European consensus.[22] It represents a subgroup of patients who do not meet the 1991 CLI criteria or in whom severely reduced flow to the foot does not present as rest pain, ischaemic ulceration, or ischaemic gangrene. Patients in this stage of "transition" between exercise-induced ischaemia and permanent critical ischaemia are nevertheless a subgroup at risk that is important to identify.[22,23] Although distal blood flow might be just sufficient to maintain skin integrity in these patients, it will probably not meet the needs of the wound healing process, which requires a higher and pulsatile flow.

4. Epidemiology

4.1. Estimated incidence and prevalence of CLI

The precise assessment and comparison of epidemiologic data on CLI is extremely difficult – almost impossible – for several reasons.

First, whereas identification of PAOD based on an ABI <0.90 is fairly easy, identification of CLI (rest pain and trophic changes attributable to PAOD) needs an expertise not readily available when evaluating large numbers of patients in the setting of epidemiological studies.

Second, data are subject to major differences between studies due to differences between definitions of CLI used in these studies. Indeed, as already mentioned above, CLI definition has evolved over time, but more importantly, a strict definition including objective haemodynamic parameters is not always used, and all patients with rest pain or trophic lesions are sometimes included without confirming the severity and causative effect of arterial insufficiency, therefore leading to higher rates of "CLI".

Third, the actual statistical data on incidence and prevalence of CLI are often inferred from two indirect markers: the overall incidence of major amputations (assuming that about 25% of CLI patients will undergo amputation) and the natural history of PAOD.[24] Both are debatable. Indeed, depending on the country, 70–90% of

amputations are considered to have a vascular cause, even though many amputations are still performed without any vascular workup.[25] Then, the natural history of PAOD does not follow a standardised progression through different clinical stages. It is estimated that 5–10% of patients with asymptomatic PAOD or claudication will progress to CLI at 5 years and that 1–3% of patients with PAOD are in CLI stage at initial presentation.[13] This latter group is often represented by older and sedentary patients who have limited mobility (and therefore do not claudicate), patients with sensory neuropathy who have impaired pain sensation, and patients with additional medical conditions reducing peripheral perfusion (such as cardiac failure), who present directly with advanced disease. Studies suggest that half of CLI patients do not present any PAOD symptoms 6 months prior to the onset of CLI.[26]

Nevertheless, the **incidence** of CLI derived from natural history of PAOD and major amputation rates has been estimated to be approximately 500–1000 per million per year in a European or North American population (150,000 cases per year for the USA).[13]

In contrast, the incidence of CLI based on large prospective population studies is 220 new cases per million per year in the general population.[27] The **prevalence** of CLI in the population aged 60–90 years is estimated at 1% (0.5–1.2%), but figures vary widely between population-based studies and vascular registries. For instance, in 2004 in Sweden, the prevalence of CLI was estimated to be at least 15,000 patients, but the number of vascular interventions for CLI was only 1700 for the same period.[28] The reported gender differences in CLI prevalence vary between studies. In series of patients with CLI, the men to women ratio is around 3:1.[13] However, in population-based epidemiological studies, age-adjusted prevalence of CLI is equal in men and women after 50 years, a finding that correlates with epidemiological studies on prevalence of PAOD based on ABI measurement.[28–30]

4.2. Risk factors for CLI

In the vast majority of cases, CLI is caused by multi-level occlusive atherosclerotic disease. Consequently, CLI patients share the same traditional risk factors as patients with atherosclerosis in other territories. Moreover, as CLI is an advanced stage of PAOD occurring late in the course of patients' atherosclerotic disease, concomitant severe cerebrovascular (CVD) and coronary artery diseases (CAD) are more frequent than in patients with claudication. Indeed, 50–75% of CLI patients have associated CVD and about 20% have associated CAD.

Among cardiovascular risk factors, some are more strongly associated with progression to CLI: threefold increase in the risk of developing CLI in the case of a long history of chronic heavy smoking and fourfold in the case of diabetes.[10,13] The risk of developing CLI rises proportionally to the number of cigarettes smoked.[31] The duration of smoking cessation needed to return to baseline risk is however not known, but is usually considered to be around 2 years in patients at risk of cardiovascular diseases. Diabetes may be known and treated or unknown and revealed by the CLI episode. In some countries in which the care of diabetic patients is less well established and generalised, CLI incidence may be 10 to 20 times higher in diabetic compared to non-diabetic patients. The true impact of diabetes is, however, difficult to assess, and the proportion of diabetic patients varies dramatically between published series of CLI, ranging from 35% to 80%. As already discussed in the preceding section, diagnosing CLI in diabetic patients is particularly challenging due to the presence of numerous confounding factors, such as sensory neuropathy and frequent infectious complications that can possibly lead to ulceration and gangrene even in the absence of any PAOD. In contrast, calcification of leg arteries (Monckeberg disease) may cause an overestimation of ankle pressure, leading to falsely reassuring results.

Increasing age is another risk factor for CLI. The mean age of CLI patients is higher than that of non-CLI patients (about 75 years) but the range is wide (35–100 years). In the elderly, the CLI event often occurs in the setting of arterial and non-arterial poly-morbid conditions. Chronic renal failure is also associated with increased risk of PAOD and CLI, as well as increased cardiovascular mortality.[32] As in diabetics, diagnosis of CLI can be difficult in the very old and in patients with chronic renal failure due to frequent calcification of leg arteries and sensory neuropathy.[33,34] African-American ethnicity may also represent a risk factor independent from other traditional atherosclerotic risk factors, based on data concerning PAOD, but there are no data specific to CLI.[35]

Some other factors can cause or lead to progression of CLI without being actual risk factors. Atheroembolic (ulcerated plaques, popliteal aneurysms) or thromboembolic (mainly cardioembolic) disease, *in situ* arterial thrombosis due to congenital or acquired hypercoagulable states, vasculitis, thromboangiitis obliterans, popliteal entrapment, or trauma can all lead to compromised distal perfusion of the extremity with the potential progression to a clinical picture of CLI. Generally, arterial insufficiency and CLI secondary to these diseases present as a more rapidly progressive disease than atherosclerotic PAOD. Although rare, some anatomical variations of leg arteries can also lead more readily to CLI in case of occlusive disease, due to altered blood-flow distribution to foot arteries. Finally, some associated conditions can represent aggravating and/or confounding factors, particularly peripheral neuropathy.

In summary, in spite of the limitations of epidemiological data, partly related to varying definitions of CLI, one thing is beyond doubt: the total cost of CLI is considerable! And as for venous ulcers and chronic venous disorders, a small percentage of cases cost more than all others due to high rates of re-interventions, amputations, comorbidities and disability. In the presence of an ageing population and increasing worldwide prevalence of diabetes, an increase in CLI incidence and prevalence is to be expected over the future decades, making it a major public health issue.

5. Clinical presentation of CLI

As mentioned above, CLI refers to the extreme stage of chronic arterial insufficiency of a lower extremity in which distal blood flow and microcirculatory function (vasomotor adaptation, capillary recruitment) are severely

compromised,[36] resulting in a clinical picture including ischaemic rest pain, ischaemic ulcer and/or gangrene as well as other clinical signs related to forefoot haemodynamic and trophic changes described in this section.

5.1. Ischaemic rest pain

According to the main guidelines and the 1991 European consensus,[11] ischaemic rest pain must be named as such if it corresponds to the description by Cranley: "ischemic rest pain is pain that occurs in the toes or in the area of the metatarsal heads. Occasionally, it occurs in the foot proximal to the metatarsal heads. Elevation of the limb above or at the horizontal position aggravates the pain and pendency, to some degree at least, brings relief".[37] In more than 90% of cases, the toes are involved. Three degrees can be described. First, the pain starts at primo-decubitus and declines quickly – the patient can thus stay supine; of note, the patient can experience numbness or tingling instead of pain. Second, the patient needs to dangle his leg to relieve the pain. Third, the patient has to remain seated to relieve the pain. In second and third degrees, dependent foot oedema develops, worsening the ischaemia because increased tissue pressure exceeds capillary pressure. It is important to bear in mind that rest pain depends on pain perception, which can be reduced or abolished in the case of sensory neuropathy (secondary to diabetes, ageing, or to ischaemia itself).

5.2. Ischaemic ulcer and gangrene

Ulcerations occurring in the context of severe ischaemia related to PAOD are located at the limb extremity, involving the toes and foot (especially on pressure areas like the heel or the first and fifth metatarsal heads). Clinically, they have an inactive edge, pale necrotic base or are covered with fibrinous material. Whereas ischaemic rest pain has a typical and standardised presentation (in the absence of sensory neuropathy), ischaemic ulcer and toe gangrene are much more difficult to identify as lesions clearly attributable to end-stage PAOD.[11,26–28] Schematically, three situations can be encountered. First, arterial insufficiency is severe, and the ischaemic skin lesion occurs spontaneously or after a minor trauma. Second, arterial insufficiency is moderate but severe enough to impair the healing process of any skin lesion (skin flow needed for wound healing is much higher than skin flow necessary for baseline nutritional requirements of an intact skin). Third, PAOD is present, but only as an associated condition, with no causal relationship with skin lesions. Even in the presence of toe gangrene, the potential morphological lesions of lower limb arteries identified by imaging techniques may be innocent if perfusion pressure remains well above threshold values for critical ischaemia. This issue is particularly important in diabetic foot lesions because of numerous potential confounding factors, and the causative link between PAOD and trophic changes should be documented with particular attention in these patients.

As a general rule, all patients with ulcers or gangrene of the extremity should first be thoroughly examined for other associated clinical signs suggestive of chronic compromised blood flow to the foot (see below). Then, an objective quantification and confirmation of the severity of foot ischaemia by distal pressure measurement and microcirculatory assessment (mainly forefoot TcPO$_2$) should be performed. This indeed seems the only way to avoid the simplifying equation "gangrene/ulcer = critical limb ischaemia".

5.3. Other clinical signs of CLI-related forefoot haemodynamic changes

Other less well known signs of CLI can easily and rapidly be assessed by simple inspection and palpation of the foot and are highly informative.

Some of these signs are related to low residual perfusion pressure and consequent vasomotor paralysis. Refilling of the foot's superficial veins after emptying with the physician's thumb and capillary refilling time at forefoot level are normally nearly instantaneous, but become more and more prolonged as arterial insufficiency becomes more severe. Also, hydrostatic pressure changes when elevating or letting the foot in a dependent position induce the following colour changes: rapid (<30 seconds) appearance of foot sole pallor by elevating the limb at 60° above bed level (Buerger's test), and foot erythrocyanosis in dangling position (also called dependent rubor).

Other signs already reflect trophic changes secondary to chronic severe ischaemia: shrinking and atrophy of the toe pulp or heel pad, with bone contact felt on palpation.[38,39]

When present, these clinical signs are predictive of severe arterial insufficiency (ABI <0.50, toe pressure <30 mmHg, forefoot TcPO$_2$ <30 mmHg in supine position; $p < 0.01$ [personal unpublished data]). On the contrary, absence of these signs makes the diagnosis of CLI unlikely. Looking for these clinical changes is thus an important part of the initial assessment of clinical probability of CLI.[40,41]

The pole test, a variant of Buerger's test, is yet another useful clinical tool to evaluate ankle or toe pressure.[16,17] It allows estimating a toe pressure <55–70 mmHg and ankle pressure <45 mmHg, and is particularly useful when calcification of leg arteries impairs accurate ankle pressure measurement and a device for toe pressure measurement is not available.

6. Natural history and prognosis

6.1. Natural history of CLI patients

CLI is a very severe medical condition with a high risk of major amputation, disability and death. In a way, it behaves like a malignant disease. In the consensus documents discussed above, as well as in review articles, the natural history of CLI patients is summarised as follows:
- At presentation: 20–25% of patients undergo primary amputation, 50–60% have vascular reconstruction (surgical and/or endovascular), and 25% are treated medically.
- One year later: 20–25% of patients will have died, 25–30% will have had major amputation, 20% will still be in CLI state, and 25% will be alive without major amputation and free from signs and symptoms of CLI.[10,13]

Although these figures are always cited in the introduction of articles published on CLI, they often do not correlate with more recent publications on CLI patients' outcome, for at least two main reasons. First, the overall management of cardiovascular patients has dramatically changed in recent years, and an increasing proportion of patients are offered "best medical treatment" and risk-factor modification counselling, which could of course partly account for a better global prognosis of CLI patients. However, there seems to be a second important reason for the discordance between prognosis data derived from original series compared to more recent series. As discussed in previous sections, inclusion criteria of many recent studies have been described as "Fontaine stage III or IV" as if it was an equivalent of CLI, without any haemodynamic criteria. Therefore, less severe patients (in terms of systemic atherosclerotic disease) might have been included in recent series, contributing to a better overall prognosis.

The TAMARIS trial probably offers the most reliable recent data on the natural history and prognosis of CLI.[21] It included patients with CLI defined according to the TASC I document, who were unsuitable for revascularisation as assessed by a vascular surgeon. Patients were randomised to an angiogenic treatment (NV1FGF) or placebo. From December 2007 to July 2009, 525 patients were included in 171 hospitals in 30 countries. No patient was lost to follow-up. The primary combined endpoint was time to major amputation of the treated leg or death from any cause during the study period of 12 months. Primary outcome was encountered in 33% (95% CI: 27–39%) of patients in the placebo group (major amputation or death 33%, major amputation 21%, death 15%). Death was from a cardiovascular cause in 49%, a non-cardiovascular cause in 41%, and unknown origin in 10%.[21]

6.2. Risk stratification

After establishing a precise diagnosis of CLI based on clinical and haemodynamic criteria, which clearly helps evaluating and comparing different treatment modalities (surgical and/or endovascular strategies, angiogenic treatments, conservative medical management, etc.) in terms of outcome and cost-effectiveness, the next step is to stratify local and general risk in order to better identify which patients benefit most from each management strategy. A prediction model derived from the BASIL study has been proposed to facilitate clinical decision-making in patients with severe ischaemia.[42] It mainly illustrates the fact that this stage of advanced PAOD is associated with high cardiovascular risk due to major comorbidities.

There is a need for risk stratification tools taking into account quantitative assessment of the degree of ischaemia. As with venous thromboembolism (VTE), we may apply the following decision process: (1) clinical probability assessment, (2) diagnostic validation, (3) risk stratification. A thorough assessment of the symptoms and signs described above establishes the clinical probability of CLI. Then, objective measurement of distal perfusion pressure (toe pressure, pole test) is needed to confirm the diagnosis of CLI,[43] with the role of additional vascular imaging being mainly to define the actual treatment strategy. Finally, the same haemodynamic measurements used for diagnosis confirmation can be used for risk stratification.

Nevertheless, the capability of distal pressure (ankle pressure and even toe pressure) to predict amputation risk is limited.[7,44–46] Forefoot TcPO$_2$, if measured according to methodological rules (particularly avoiding areas of thick or oedematous skin) is probably the best non-invasive method for quantification of ischaemia severity and prognostic assessment.[41] Forefoot TcPO$_2$ may be considered a marker of total distal run-off (arterial and arteriolar run-off) and perfusion reserve. In the setting of risk stratification, different values have been suggested, but almost all series are in agreement with the following criteria: in case of supine forefoot TcPO$_2$ >35–40 mmHg, local prognosis is fairly good even with conservative management, and these patients can therefore not be truly considered to have CLI; in case of supine forefoot TcPO$_2$ 10–35 mmHg, local prognosis is intermediate; in case of supine forefoot TcPO$_2$ ⩽10 mmHg (which corresponds to the 1991 European consensus document's recommendation for the diagnosis of CLI[11]), local prognosis is very poor. Of note, further prognostic stratification of patients with low supine forefoot TcPO$_2$ (<20 mmHg) can be performed by testing perfusion reserve in sitting position or under oxygen inhalation (oxygen inhalation being more efficient when performed in sitting position).[46,47]

In a personal prospective series of 205 patients with CLI defined according to the 1991 European consensus with supine forefoot TcPO$_2$ ⩽10 mmHg, all operated on (bypass surgery and/or PTA) with a follow-up >1 year, the overall rate of major amputation-free survival at 1 year was 50%. It was 75% in case of TcPO$_2$ improvement in sitting position (to ⩾40 mmHg) and only 35% if TcPO$_2$ remained <40 mmHg in sitting position.[46]

Data are insufficient to give a grade A recommendation, but seem enough to give a grade B recommendation for a baseline risk stratification scale (major amputation or death) in four degrees, based on forefoot TcPO$_2$ in addition to initial careful clinical examination.

- <u>Degree 1</u>: 10 mmHg < forefoot TcPO$_2$ ⩽35 mmHg in supine position.
- <u>Degree 2</u>: forefoot TcPO$_2$ ⩽10 mmHg in supine position but clear improvement (⩾40 mmHg) in sitting position or under oxygen inhalation.
- <u>Degree 3</u>: forefoot TcPO$_2$ ⩽10 mmHg in supine position and inadequate or no improvement (<30–40 mmHg) in sitting position or under oxygen inhalation.
- <u>Degree 4</u>: forefoot TcPO$_2$ ⩽10 mmHg in supine and in sitting position and/or under oxygen inhalation (very poor prognosis).

7. Conclusion and recommendations

As CLI prevalence is expected to increase over the future decades and become a major public health issue, it is of utmost importance to bear in mind some major key points that help to characterise patients with precision in order to assess and compare current or future treatment modalities. These can be summarised as follows:

Recommendations

(1) The expression chronic critical limb ischaemia (CLI) defines the extreme stage of chronic arterial insufficiency of a lower limb in which stenosis and/or occlusion of the arterial tree lower the downstream perfusion pressure to such an extent that nutritional flow to tissues is severely compromised and does not allow maintaining skin integrity or wound healing without revascularisation. **(Level 1a; Grade A)**

(2) The presence of rest pain or a wound, ulcer or toe gangrene on a lower limb with arterial disease (PAOD) is not sufficient to qualify as CLI. They must be recognised as **attributable to** the PAOD by combining specific clinical characteristics of pain and/or skin lesions, as well as other signs of severe chronic forefoot ischaemia, with objective haemodynamic measurements. **(Level 2b; Grade B)**

(3) Ankle systolic pressure (absolute value or ABI) is not a reliable parameter for CLI diagnosis. **(Level 2b; Grade B)**

(4) Toe pressure measurement is more accurate and is recommended in all patients with suspected CLI. **(Level 2b; Grade B)**

(5) Assessment of distal tissue perfusion pressure by forefoot TcPO$_2$ measurement should be recommended for diagnostic validation and prognostic stratification, at least in the setting of clinical trials. **(Level 2b; Grade B)**

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None

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