Urgent need to clarify the definition of chronic critical limb ischemia - a position paper from the European Society for Vascular Medicine

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A position paper from the European Society for Vascular Medicine

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Abstract

Chronic critical lower limb ischemia (CLI) has been defined as ischemia that endangers the leg. An attempt was made to give a precise definition of CLI, based on clinical and hemodynamic data (Second European Consensus). CLI may be easily defined from a clinical point of view as rest pain of the distal foot or gangrene or ulceration. It is probably useful to add leg ulcers of other origin which do not heal because of severe ischemia, and to consider the impact of frailty on adverse outcome. From a hemodynamic viewpoint there is no consensus and most of the existing classifications are not based upon evidence. We should thus propose a definition and then validate it in a prospective cohort in order to define the patients at major risk of amputation, and also to define the categories of patients whose prognosis is improved by revascularisation. From today's available data, it seems clear that the patients with a systolic toe pressure (STP) below 30 mmHg must be revascularised whenever possible. However other patients with clinically suspected CLI and STP above 30 mm Hg must be evaluated and treated in specialised vascular units and revascularisation has to be discussed on a case by case basis, taking into account other data such as the WiFi classification for ulcers.

In conclusion, many useful but at times contradictory definitions of CLI have been suggested. Only a few have taken into account evidence, and none have been validated prospectively. This paper aims to address this and to give notice that a CLI registry within Europe will be set up to prospectively validate, or not, the previous and suggested definitions of CLI.

Chronic critical lower limb ischemia (CLI) has been defined as ischemia that endangers the leg (1). This concept was first proposed in 1982 by a Working Party of the International Vascular Symposium (2). The concept of acute ischemia of the limb is easy to process but the problem is far more difficult for CLI. The leg is endangered when significant ischemia happens at rest and causes symptoms. The clinical picture is made up of rest pain affecting the distal part of the foot, and wounds, ulcers or even necrosis. Necrosis and some ulcers are recognised as being caused by arterial issues (reduced blood supply) but arterial disease may also be responsible for slow or absent cicatrisation of a leg ulcer caused by venous insufficiency. Assessment of the role of arterial disease in any kind of wound is a key area because of the dramatic progress during the last decade in revascularisation techniques. Proving arterial disease is present is not difficult, conversely proving that arterial disease is responsible for symptoms is far more difficult. In the present article we will review existing guidelines surrounding the definition of CLI and we will define the position of the European Society of Vascular Medicine on the subject.

Background: guidelines on chronic critical limb ischemia (Table 1???)

European consensus documents on critical limb ischemia

The first European consensus defined CLI in patients without diabetes as "persistently recurring rest pain requiring regular analgesia for more than 2 weeks, or ulceration or gangrene of the foot, plus a systolic ankle pressure (SAP) ≤50 mm Hg" (3). A strict definition was crucial to allow different treatments and results to be compared from different centers and to give information about prognosis to the patient (4). A second consensus document provided a definition of CLI in patients with and without diabetes. The clinical part of the definition was the same but systolic toe pressure (STP) ≤30 mm Hg was added as an alternative to ankle pressure ≤50 mm Hg (1) . It was suggested that patients be more precisely described by measuring STP in all patients including those without diabetes and by measuring transcutaneous tissue oxygen pressure (TcPO2) (1). Shortly after this classification was proposed, Thompson (5) suggested a re-definition of CLI because they found that SAP ≤50 mm Hg was unable to differentiate patients in terms of prognosis for limb salvage at one year) in a series of 133 patients with 148 ischaemic limbs. This article confirmed the inability of SAP to define CLI.

Recommended standards for reports dealing with lower extremity ischemia (Rutherford category)

Rutherford (6).proposed a definition and classification criteria where class 4 was ischemic rest pain, class 5 was minor tissue loss and class 6 major tissue loss. He proposed a SAP<40 mm Hg or STP<30 mm Hg for class 4, and SAP<60 mm Hg or STP<40 mm Hg for classes 5 and 6 as objective criteria to be associated with clinical presentation criteria. These criteria were not very different from those of the second European consensus[ref needed] but addressed tissue loss with less severe ischemia. He considered that different criteria have to be used for patients with rest pain or tissue loss because of the difference between the levels of perfusion pressure required to preserve intact tissue or prevent ischemic rest pain, and especially because of the additional circulatory requirement for the healing of ischemic foot lesions.

TASC and TASC II guidelines (7) (8)

- The TASC clinical definition was: chronic ischemic rest pain, ulcers, or gangrene attributable to objectively proven arterial occlusive disease. The aim of the hemodynamic parameters included in the definition was to ensure that the ulceration, gangrene, or rest pain was indeed caused by peripheral arterial disease and that most would be expected to require a major amputation within the next 6 – 12 months in the absence of a significant hemodynamic improvement. To achieve this hemodynamic picture, it was suggested to use either absolute ankle pressure < 50-70 mm Hg or STP ≤30-50 mm Hg or TcPO2 ≤30-50 mm Hg.
- TASC II indicated that CLI is a clinical diagnosis but should be supported by objective tests (8). TASC II considered that ischemic rest pain most commonly occurs below SAP of 50 mmHg or STP less than 30 mmHg. It stated that healing requires an inflammatory response and additional perfusion above that required for supporting intact skin and underlying tissues. The ankle and toe pressure levels needed for healing are, therefore, higher than the pressures found in ischemic rest pain. For patients with ulcers or gangrene, the presence of CLI was suggested by an ankle pressure less than 70 mmHg or a toe systolic pressure less than 50 mmHg (8).

European Society of Vascular Surgery 2011

In 2011, Becker et al for the European Society of Vascular Surgery considered that the thresholds for toe pressure and TcPO2 proposed by TASC 2 were just below the lower limit of normality and inferred that patients categorized as CLI by TASC II patients can suffer from less severe disease than those qualifying as CLI using the second European consensus definition (9). They recommended toe pressure measurement in all patients with suspected CLI and they stated that

ankle systolic pressure (absolute value or ankle brachial index) is not a reliable parameter for CLI diagnosis. They also proposed that one could stratify the risk of amputation with TcPO2.

Society for Vascular Surgery wound, ischemia and foot infection threatened limb classification system (Wifi Classification)

The Society for Vascular Surgery developed a classification of the lower extremity that reflects wound extent, severity of infection and abnormal arterial perfusion (10). In this classification, ischemia was defined from grade 0 to 3 according to hemodynamic measurements. Grade 3 was defined by ankle brachial index (ABI) <0.39, SAP ≤50 mm Hg or STP≤30 mm Hg. This classification underlined that other factors may contribute to the prognosis of an ischemic foot. The WiFi classification system predicted the amputation risk and survival in a highly selected group of CLI patients without diabetes treated by endovascular means, with a statistically significant difference between very low-risk and high-risk patients at 1 year (11). Although this classification is useful in adding characteristics of the wound to predict prognosis, this scoring system is complex and uses the term 'ischemia' for values of SAP between 70 and 100 mm Hg or toe pressure or TcPO2 <60 mm Hg. Even though this classification has been validated, the role of ischemia is unclear in the patients classified as high risk because of "wound 2" (deep ulcer with exposed structures) and "ischemia 1". Delayed ulcer healing has not been demonstrated so far in "wound 2" patients between those with STP between 50 and 60 or above 60 mm Hg. This classification system is widely used nowadays in clinical trials with CLI. It allows inclusion of more patients into clinical trials than would occur with other definitions.

American heart Association (AHA) recommendations

The AHA recommendations defined CLI as "a condition characterized by chronic (≥2 weeks) ischemic rest pain, non-healing wound/ulcers, or gangrene in one or both legs attributable to objectively proven arterial occlusive disease" (12). The diagnosis of CLI was described as a constellation of both symptoms and signs. Arterial disease could be proved objectively with measures of ABI, toe brachial index (TBI), TcPO2, or skin perfusion pressure (SPP).

In patients with normal (1.00–1.40) or borderline (0.91–0.99) ABIs in the setting of non-healing wounds or gangrene, it was considered reasonable to diagnose CLI by using TBI with waveforms, transcutaneous oxygen pressure (TcPO2), or SPP. In patients with PAD with an abnormal ABI (<0.90) or with non compressible arteries (ABI >1.40 and TBI <0.70) in the setting of non-healing wounds or gangrene, TBI with waveforms, TcPO2, or SPP could be useful to evaluate local perfusion. These recommendations just address the diagnosis of arterial disease but do not suggest any hemodynamic

value to attribute rest symptoms to PAD. This definition of CLI, however, is not based on any objective testing.

Not sure what message you want to give with above paragraph

2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases,

in collaboration with the European Society for Vascular Surgery (ESVS)

These recommendations introduced a new term: "limb threatening ischemia" that did not clarify the debate (13). They proposed to use the Wifi system for the initial assessment of all patients with ischemic rest pain or wounds. The target population for this system includes any patient with ischemic rest pain, typically in the forefoot with objectively confirmed hemodynamic studies (ABI <0.40, ankle pressure<50mmHg, toe pressure <30mmHg, TcPO2 <30mmHg), diabetic foot ulcer, non-healing lower limb or foot ulceration ≥2weeks duration or gangrene involving any portion of the foot or lower limb. It is paradoxical not to define any objective hemodynamic threshold for diabetic foot ulcers that may occur in the absence of any significant foot ischemia. These recommendations introduce the term of 'limb threatening ischemia' without any precise definition

European Society of vascular medicine (ESVM) recommendations on lower limb arterial disease

The ESVM defined categories of PAD severity after ABI. ABI<0.50 defined CLI but it was stated that this classification is only valid in the absence of arteriosclerosis ??????? (in press). If arteriosclerosis was suspected, ESVM strongly recommended the toe pressure measurement.

Need for a new definition of CLI

Since a restrictive but rigorous early definition(1), the concept of CLI has become blurred into a more and more unclear term, and even confounded by new expressions such as 'limb threatening ischemia'. It is now urgently required to provide a definition that can be used by all clinicians.

From the the clinical aspect all the proposed definitions are similar. CLI may be easily defined from a clinical point of view as rest pain of the distal foot or gangrene or ulceration. It is probably useful to add leg ulcers of other origin which do not heal because of severe ischemia, and to consider the impact of frailty on adverse outcome. For hemodynamics there is no consensus but most of the existing classifications are not evidence-based. We should thus propose a definition which is then validated in a prospective cohort in order to define the patients at major risk of amputation, and also to define the categories of patients whose prognosis is improved by revascularisation. The patients defined as CLI according to TASC 2 but not by the Second European Consensus in the COPART cohort had fewer

major amputations at one year than those who fulfilled both definitions. (14). Ankle pressure and ankle brachial index fail to identify CLI, especially in patients with diabetes because of arterial calcification (15). Thompson found that SAP was not associated with the risk of further amputation(5). Sukul recently found substantial heterogeneity in pre-revascularisation ABIs (16). He suggested that the disconnect between ABI results and clinical diagnosis calls into question the utility of ABIs in this population and suggests the need for standardization of functional PAD testing (16). In a recent work in 556 patients from the COPART cohort, SAP <70 mm Hg failed to detect 42% of the patients with CLI proven by STP or TcPO2 (17). Moreover there was no association between low SAP or ABI and the risk of major amputation. In contrast, STP<30 mm Hg predicted the risk of amputation in the whole population (OR 3.5) as well as in the patients in whom revascularization had failed or was impossible. TcPO2<10 mm Hg also predicted major amputation (OR 2.3 and 3.8 respectively), as well as TcPO2 <30 mm Hg (OR 3 in both groups). The risk of major amputation was not increased in the patients with STP between 30 and 50 mm Hg versus those with STP>50 mm Hg, suggesting 30 mm Hg as the best threshold for STP. TcPO2<30 mm Hg seems to be clearly associated with an increased risk of amputation. The best method to predict amputation was STP as assessed by ROC curves. STP must be the preferred measure because TcPO2 may be hampered by edema and thus be difficult to measure. The validated method for STP measurement is laser Doppler. Other methods such as photo-plethysmography may be used but their validity for CLI diagnosis is uncertain because of the difficulty in detecting low pressures (18). Other methods such as Near Infra-Red Spectroscopy (NIRS) might be useful but should be further investigated (19). Reliability of systolic perfusion pressure (SPP) is questionable (20).

Proposed strategy to diagnose CLI

Today STP measurement is not widely available and thus the first step is to identify those patients with suspected CLI who must be referred to a vascular center for this measure. In patients without diabetes with no renal insufficiency, SAP may be used a first widely available tool to screen the patients who need to be referred to a vascular medicine unit. Vascular units should use STP to assess CLI in all patients. Patients with diabetes or renal insufficiency should be directly referred to vascular specialists as soon as CLI is suspected. A clear and consensual definition should be proposed for CLI, including hemodynamic criteria. STP should be a key method for the hemodynamic part of the definition today. This consensual definition is not available at the moment but should be a working objective for ESVM and European Society of Vascular Surgery (ESVS).

Another point is actually how useful is the CLI concept. From today's available data, it seems clear that the patients with STP below 30 mm Hg must be revascularized whenever possible. However other patients with clinically suspected CLI and STP above 30 mm Hg must be evaluated and treated in

specialized vascular units and revascularisation has to be discussed on a case by case basis, taking into account other data such as the WiFi classification for ulcers.

In conclusion, many useful but at times contradictory definitions of CLI have been suggested. Only a few have taken into account evidence, and none have been validated prospectively. This paper aims to address this and to give notice that a CLI registry within Europe will be set up to prospectively validate, or not, the previous and suggested definitions of CLI.

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