Roberto Ferraresi

Critical limb ischaemia: treatment protocols and latest trends in management

Critical limb ischaemia (CLI) is a serious disorder of the lower limbs that frequently results in amputation or death. *Confluence* spoke to Dr Roberto Ferraresi, Istituto Clinico Citta Studi, Milan, Italy, about how best to manage these challenging patients.

Could you define what we mean by CLI?

The definition of CLI is apparently quite clear: pain at rest and/or a tissue lesion, either of which are related to obstruction(s) of the vessel tree of the inferior limb.

Today, the main problem with this definition of CLI is that it predominantly refers to a non-diabetic patient population. If you look at the two most important classifications of the manifestation of peripheral artery disease, the Fontaine[1] and the Rutherford[2] classifications, we see clearly that the development of CLI is described as an evolution from asymptomatic to claudication, rest pain and tissue loss. However, we must consider that the Fontaine classification was published in 1954, when the prevalence of diabetes, in the USA for example, was less than 1%. Even by the publication of Rutherford's classification in 1991, the prevalence of diabetes was 2.9% in the USA, so clearly these types of classification are related to non-diabetic patients, rather than diabetic patients.

Nowadays, the situation is completely different because of a huge increase in diabetes all over the world. It was estimated that in 2030 there would be about 460 million people with diabetes in the world, but this may be an underestimate. This is critical because more than 60% of CLI patients are diabetics,[3] and in diabetic patients the natural history of CLI is different.

Do patients with diabetes and CLI present in similar ways?

No. The first reason is that the disease in diabetics is more distal, involving the below-the-knee (BTK) vessels and the foot vessels. The second reason is that less than 25% of diabetics with peripheral artery disease report intermittent claudication, and we also know that pain at rest is less frequently reported in diabetics than in non-diabetic patients.[4]

In non-diabetic patients, there is evolution of the obstructive disease of which CLI is the final manifestation of the terminal failure of blood supply. In diabetics the situation is different because in the majority of cases they are completely asymptomatic before the emergence of tissue lesions. However, when you look at the vessels you can see multi-level disease with a prevalence of occlusion or stenosis and you can see a predominantly distal disease, so you must consider that this patient was asymptomatic, but with a chronically ischaemic foot. The TransAtlantic InterSociety Consensus (TASC) II document describes this as subclinical critical ischaemia. I prefer the term 'foot hibernation'.

In the majority of diabetic patients the onset of tissue lesions is unrelated to the progressive increase of obstruction of the arterial tree, but is due instead to mechanical trauma and neuropathy. We have a chronic evolution of disease, but the foot is able to survive for many years. Patients with diabetic neuropathy have poor feeling in their foot and can easily damage the tissue because of foot deformity, peak pressure on the metatarsal heads, poorly fitting shoes, foreign body in the shoes, hot water burns, incorrect nail care, etc. It is only after trauma that the foot suddenly requires a considerably increased blood supply for healing and, due to the disease, the vascular tree is unable to support this need.

What other risk factors are associated with the disease?

Other risk factors include smoking, hypertension and hypercholesterolemia; however, these risk factors are related to a different type of disease that is predominantly localized in the big arteries, rather than the small distal arteries, a disease which has an evolution according to the Fontaine and

Rutherford classification – so it is completely different.

How does the histology of peripheral artery disease differ from coronary disease?

One of the main problems is that classification of different forms of atherosclerotic disease is poor. We talk about atherosclerotic disease associated with the coronary artery, aorta, iliac artery or BTK vessels, but histologically the diseases are different.

In diabetic CLI, involving diffusely the BTK vessels, we cannot think in terms of the fibro-lipidic plaques, as in coronary arteries; we have some components that are completely different, diffuse inflammatory infiltration in the vessel wall and diffuse calcification. This is especially important in patients with end-stage renal disease on haemodialysis. They often have a considerable calcification of the small vessels with a diffuse "bone-fication" of the arterial tree.

Once a patient has been diagnosed with CLI, what is the aim of treatment?

Healing is a blood flow-dependent phenomenon and the first principal in our revascularization strategy must be giving the best possible blood supply to the foot. Faglia and Peregrin have demonstrated that complete revascularization is better than partial revascularization in the BTK vessels.[5,6] They showed that angioplasty of tibial arteries had a better outcome than angioplasty of the peroneal artery alone, so complete revascularization is our first target. Limb salvage rate at one year increased from 56% without direct blood flow to the foot (zero BTK vessels open) to 73%, 80% and 83% with one, two or three BTK vessels open.

The second important principal is the concept of the angiosome-oriented angiopathy, the so-called 'wound-related artery'. There are a lot of papers now about this concept; the first paper by Neville, regarding direct revascularization of a specific angiosome directly feeding the lesion-specific angiosome, and the papers by Iida and Alexandrescu about angioplasty of the wound-related artery.[7-11] It was claimed that angiosome-targeted revascularization led to higher rates of wound healing and wound salvage than did indirect revascularization.

However, there are a number of criticisms of this concept: firstly, all of the studies comparing direct and indirect revascularization are retrospective with possible bias in case selection; secondly, the presence or absence of a good distal distribution network could affect the value of direct revascularization i.e., the distal distribution system is reduced or absent in patients with diabetes or end-stage renal disease patients so the wound-related artery could have different value depending on the presence or not of small vessel disease; finally, not every wound, especially in the case of deep infection, is confined to a single angiosome space – patients with extensive tissue damage cannot be classified on the basis of an angiosome-oriented revascularization. In conclusion, I think that we must balance the strategy of our revascularization, considering the technically realistic targets, the foot conditions and the patient's overall condition: better to tailor the procedure to the specific patient, rather than adhere strictly to the wound-related artery or complete revascularization approaches.

How do you carry out the revascularization?

I very much like the use of a drug-eluting balloon (DEB) to treat CLI. The average length of a BTK lesion I treat is more than 18 cm. This is a considerable length of vessel, so I think that drug-eluting stents are not a sensible option, especially because focal lesions tend to be very rare, at least in my population. Today, DEBs are the only devices able to guarantee a good patency for this type of patient. Other procedures such as atherectomy tend to be excessively expensive and time consuming.

We know that patients can have other conditions associated with this disease that require medical and surgical management. How is this organized?

We follow a rigorous protocol that depends on the infection status of the patient.

For Texas University Classification Type C lesion (ischaemia without infection) patients, we start with a global medical evaluation and treatment (glycaemia control, prophylactic management for renal failure, dual antiplatelet therapy). The second step after medical preparation is the revascularization therapy. The third step is the final surgical treatment of the foot.

Our protocol for patients with infection and ischaemia (Texas University Classification Type D

lesion) is completely different because we believe that infection is the main problem, jeopardising not only the limb but also the life of the patient. Therefore, surgical debridement of the infected ulcers and surgical drainage of abscess and phlegmon is the first step. This is so critical that we have a 24-hour surgical room for emergency surgery of the foot. We treat every foot infection as an emergency. After the surgical treatment, medical therapy (antibiotic therapy, prophylaxis for renal disease, etc.) is necessary. The third step is revascularization and after that we have the final surgical treatment. The goal is always to give to the foot some capacity to walk again. The knowledge of the biomechanics of the foot is essential, we work together (foot surgeon, orthopaedic, podiatrist, physiotherapist) to try and ensure that patients retain as much mobility as possible.

It sounds like multidisciplinary care is very important. Who should be involved?

It is a complex approach involving three teams. First of all the "medical team": diabetologists, nephrologists, cardiologists, infectologists and neurologists. A nephrologist is essential because nowadays about 30% of our patients are receiving haemodialysis. The second team is the "toe team", which comprises the foot surgeon and the podiatrist, but we also work with orthopaedic and plastic surgeons, as necessary. Finally, we have the "flow team". I am an interventional cardiologist but you can have an interventional radiologist or a vascular surgeon performing the endovascular treatment, and you also need vascular surgeons for bypass and thromboendarterectomy. You need these three types of team working together around the same table to provide the patient with a multidisciplinary and complete treatment.

In our centre, we have all grown into our roles. I was a cardiologist, but in the last 15 years I have progressively increased the number of CLI patients I treat. Our foot surgeon was a diabetologist, but nowadays he performs about 1,000 surgical procedures on diabetic feet every year, including very complex orthopaedic reconstruction of the foot. So single specialists are not important – it is the skills that you bring and how you work together, rather than your title, that is important.

What outcomes can be expected following treatment?

This is a very complex topic because of the variety of patients and wounds that we see. You must probably tailor your outcome expectations to the single patients.

For example, consider an 85-year-old bed-ridden man with a long history of heart disease, low ejection fraction and chronic low cardiac output. Here, CLI may be the expression of very mild or moderate arterial disease with a low output by the heart and likely represents the final stage of life for this patient. Therefore, it is like the final stage of a cancer, our expectation can be only palliative care. Try to reduce pain, manage the infection – if possible – nothing more because this is a patient that will never be able to walk again, so treatment would not be beneficial.

Now consider a 65-year-old mobile patient with a history of diabetes. We need to put a lot of effort in to help this patient to walk again and be active. If, however, we have a 40-year-old patient with a long history of Type 1 diabetes, on haemodialysis and with complete calcification of every vessel, this is more similar to the first patient. They are at the end of their life but as he is young, you should make every effort to increase the possibility of survival of this patient by six months or more.

How important is it to treat CLI quickly?

I think this is fundamental. We all know the saying regarding myocardial infarction – "time is muscle". A similarly rapid response is required in stroke.

In CLI, we are happy when we can perform only a minor amputation – that is madness! If the patient would have come to our centre six months prior to that, the patient would probably not have required an amputation. CLI must often be treated on an emergency basis. We must diagnose and treat it immediately. An infection can spread into the foot spaces and can completely destroy the foot in a matter of hours. So the earlier we can treat an infection, the better the outcome of the patients in terms of tissue salvage. Unfortunately, it is very difficult to change the culture of physicians.

When a woman feels a nodule in her breast, the patient will have all the haematological examination tests, a mammography, an echography, a tomography of all the body and an evaluation by an oncologist within two weeks. Now think about a 65-year-old diabetic patient, with an infected lesion on one toe: not the patient, nor the family, nor the physician knows that this patient has exactly the same life expectancy as the woman with the lump in her breast. However, this

manifestation of CLI in a patient with multi-level obstructive disease of the arteries and a long history of diabetes means their life expectancy is the same as a patient with breast or prostate cancer.

We must completely change our way of thinking and we must concentrate our efforts on patients with a good life expectancy to improve their lives and to improve the quantity and quality of life. This can be done only if we understand that we must face CLI working together.

What advances are required to better manage CLI?

Recent advances in CLI have been led by advancements in technology and we now have many studies about various drug-eluting and non-drug-eluting stents and balloons, as well as other techniques; however, as I mentioned previously, we still do not have a classification of atherosclerotic disease. This is important. I think it is time the science behind CLI caught up with the therapeutic developments. This will help to ensure that the correct therapies are used in the right patients. Without clear guidelines about the causes of atherosclerotic disease, and without a clear understanding of the differences in pathophysiology in both diabetic and non-diabetic patients, we will not be able to define the best management strategy for each individual patient.

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