

Critical Limb Ischemia

Takehisa Iwai, MD, PhD

Introduction

I wish to address the problems and perspectives of critical limb ischemia, which has become a topical issue.

Why is critical limb ischemia such an important issue now? At the outset of the 21st century, gene therapy and regenerative medicine are increasingly drawing attention. In the beginning field of clinical research, however, it is important to clearly demonstrate the results of such research. Critical limb ischemia is an ideal research target, in that its treatment outcome is clear-cut, ending in either limb amputation or functional limb salvage. Currently, there is use of growth factors such as hepatocyte growth factor (HGF) and vascular endothelial growth factor (VEGF) utilised in the form of genes or via viral vectors as an intramuscular injection into the leg and lower thigh. At our hospital, some investigators have been studying injection of blood mononuclear cells or bone marrow cells from the iliac crest and have reported some good results. In the future, such research may contribute to gene and cell therapy in the heart and brain. If efficacy can be demonstrated objectively, these methods may be utilised on the treatment of inoperable intermittent claudication.

What is Critical Limb Ischemia?

It is not possible to determine the severity of ischemia based solely on the blackness or coldness of the leg. While it is estimated that 30-40% of ulcers may heal spontaneously, it is also well established that nearly 60% are healed within 1-2 months after treatment with antithrombotics such as antiplatelet agents. European reports classify cases into critical limb ischemia, resulting in limb amputation if no immediate procedure is taken, and non-critical or subcritical limb ischemia. However, since it is difficult to

From Division of Vascular Surgery, Graduate School of Medicine and Dentistry, Tokyo Medical and Dental University, Tokyo, Japan

Address reprint requests to Takehisa Iwai, MD, PhD: Professor of Surgery, Division of Vascular Surgery, Graduate School of Medicine and Dentistry, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan.

distinguish the difference, we diagnose critical limb ischemia when intolerable pain persists for over two weeks, or ankle pressure is 50 mmHg or less. For more objective scientific diagnosis, we have also proposed the measurement of transcutaneous partial pressure of oxygen, which has relatively high reliability and reproducibility. When the transcutaneous partial pressure of oxygen is 10 mmHg or less and does not increase above 10 mmHg by oxygen inhalation, we consider the situation as critical limb ischemia. According to these criteria, we have managed nearly 100 patients, reinforcing our conclusion that these are valid diagnostic parameters.

Reviewing the Fontaine Classification

Currently, the Fontaine classification is one of the most well known classifications. However, this classification was not cited in "Vascular Surgery," the Japan Surgery System edited by Seiji Kimoto in 1968, or "Introductory Book for Vascular Surgery," authored by Yoshio Mishima in 1975. It was authored in "Surgical Therapy of Peripheral Vascular Insufficiency," by Fontaine in 1954, classifying the severity of vascular insufficiency into 4 stages (I, asymptomatic; II, intermittent claudication; III, rest pain; IV, ulcer/gangrene). When quoted by Professor Shukichi Sakaguchi (then at Hamamatsu University School of Medicine) in 1979 in Japan, he added coldness, numbness, and Raynaud's symptom to class I, provoking some confusion. In the "New Surgery System" published in 1990, the neurologic symptom of numbness was added. Coldness and Raynaud's symptom were confused with excessive sensitivity to cold and Raynaud's syndrome included collagen diseases. At present, the TransAtlantic Inter-Society Consensus (TASC), a diagnostic and therapeutic guideline, combined the Fontaine classification with the Rutherford classification of the US as the criteria in 2000, re-defining degree I of class I as asymptomatic.

Which Type of Limb Ischemia is more Likely to Become Critical?

The disease is gradually progressing while the patient is

complaining of intermittent claudication. Progression is accelerated by smoking, ill-controlled diabetes/hypertension/hyperlipidemia, and obesity. In patients receiving hemodialysis, the disease is more likely to become critical and is often associated with serious complications such as sudden death. In addition, patients have difficulty in walking, becoming confined to home. As a result, activities are restricted, contributing to further progression of the disease. Patients may be worried in private that they cannot gain sufficient sympathy from their families or acquaintances because few noticeable changes may be seen in the color of the legs. However, it is said that approximately 1% of patients with intermittent claudication develop critical limb ischemia requiring limb amputation. In 1989, McDaniel reported an amputation rate of 4%. In Japan, while limited data is available, there is a report of an approximate 1% rate of amputation annually in the Osaka area for established limb ischemia.

Problems that Patients with Critical Limb Ischemia have to Confront

It remains unknown why arteriosclerosis causes the occlusion of arteries, and what triggers the occlusion. The three most prevalent sites of occlusion are the origin of the internal carotid arteries, the coronary arteries, and the peripheral arteries descending from the abdominal aorta, resulting in cerebral stroke, myocardial infarction, and lower limb ischemia, respectively. With regard to the onset, DeBailey et al. have provided data indicating that in general, cardiac ischemia is followed by lower limb ischemia and then cerebral ischemia. In our hospital, 15 patients have developed ischemia at these three sites, which may be termed "Systemic ischemia," during the last 2-3 year period. Three of them underwent operations at all three sites. This may indicate that the condition in Japan may be similar to that seen in the US and Europe. Approximately 4% of patients may require operation on for three ischemic lesion sites.

How to Save the Limb?

Critical limb ischemia may result in limb amputation

unless treated immediately after diagnosis. It is recommended that the patient is referred to a specialist as soon as the diagnosis is established or if there is uncertainty over the diagnosis. The treatment of critical limb ischemia is broadly classified into three groups. Previously-mentioned regenerative therapy is not an option for emergency situations because it takes at least one month until a new blood vessel is generated. Therefore, revascularization comprises the mainstream of the treatment. Since the condition is often associated with multiple occlusions, a crisis can be temporarily staved off by treating only the most important lesion. The treatment options are 1) To increase the blood flow by widening a narrowed iliac artery with transcatheter angioplasty and if possible, inserting a stent. It should be noted that this is applicable to stenosis or short occlusion of the iliac artery. 2) To increase the blood flow by widening the internal iliac artery or the origin of profunda femoris artery with thromboendarterectomy or patch plasty. Thromboendarterectomy is also a good choice for focal occlusion of the common femoral artery because the symptoms may be readily worsened. This procedure may be used in the aorta, common iliac artery, and external iliac artery, but bypass surgery may be a more suitable choice for lesions in these blood vessels. 3) Bypass surgeries. A simpler bypass is better, requiring high-quality angiography and arterial digital subtraction angiography. Even after successful revascularization, multidisciplinary cooperation with plastic and orthopedic surgery for partial amputation and muscle cutaneous flaps as well as rehabilitation is essential. Psychological support will also be required.

Conclusion

With the aging population, vascular disease is becoming more common. While lifestyle is fundamentally to blame to a large extent, genetic factors can also be implicated. Unless the patient is cooperative about tackling his or her lifestyle-related factors, medical science can not fully deal with the patient's condition. Therefore, it may be most important to treat critical limb ischemia in a well-timed manner.