Impact of Demographic Changes on the Natural Course, Features and Prognosis of Critical Limb Ischemia

Nobuyoshi Azuma, MD, PhD

The global pandemic of diabetes has greatly affected the pathology of peripheral arterial disease (PAD) in terms of the localization of the arterial lesion and the manifesting symptoms. Both vascular specialists and physicians who care for diabetic patients and patients with cardiovascular disease should recognize these demographic changes influencing the diagnosis of PAD. The key to the diagnosis is discerning how the symptoms are related to objective ischemia. The Fontaine classification or Rutherford category has been used as a grading system for limb ischemia symptoms. The TASC working group has defined critical limb ischemia (CLI) as follows: chronic ischemic rest pain, ulcers or gangrene attributable to objectively proven arterial occlusive disease defined by objective criteria of absolute pressures such as ankle pressure, toe pressure, and transcutaneous partial pressure of oxygen.1 In short, to diagnose CLI both the symptoms and objective ischemia proven by pressure measurements are required. However, it is possible to encounter patients who do not satisfy both conditions. In actual clinical settings, it is already known that patients with severe limb ischemia proven by objective pressure measurement but without either claudication or other ischemic symptoms do exist. Mätzke and Lepäntalo report that 37% of CLI patients did not experience claudication prior to developing CLI.2 Rutherford used the term “chronic subcritical limb ischemia” for a particular group of asymptomatic patients with severe ischemic limbs that would easily fall into Rutherford category 5 with a minor trauma.3 The TASC working group also proposed the concept of chronic subcritical limb ischemia as high-risk patients not covered by current criteria for CLI. The TASC II working group used the term “chronic subclinical limb ischemia” (CSLI) instead of chronic subcritical limb ischemia and stated that “many patients who present with CLI are asymptomatic prior to its development, but research in this area is lacking.”4

In this issue of the Journal, Shirasu et al5 focus on the symptoms prior to the manifestation of CLI, and retrospectively analyzed 225 patients with CLI. They report that 63% of patients did not experience intermittent claudication prior to the onset of CLI. They also sub-analyzed 140 CLI patients who underwent revascularization, and 54% of those patients did not experience claudication. Recently, Takahara et al published data from a multicenter prospective CLI study in Japan, and 281 patients (50%) did not experience claudication before the onset of CLI.6 These studies suggest that half or more of CLI patients in Japan may be categorized as having CSLI before manifesting CLI (Table). In the background of published serial researches and guidelines in terms of asymptomatic PAD involving CSLI, there has been renewed interest in CSLI reflecting recent demographic changes.5–7

<table>
<thead>
<tr>
<th>Country</th>
<th>Authors (year)</th>
<th>Features of non-claudicant CLI patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td>Mätzke et al2 (2001)</td>
<td>Higher Rutherford category, non-smoker</td>
</tr>
<tr>
<td>Japan</td>
<td>Shirasu et al6 (2015)</td>
<td>Higher Rutherford category, diabetes, non-ambulatory, distal arterial lesion, hypoalbuminemia</td>
</tr>
<tr>
<td>Japan</td>
<td>Takahara et al6 SPINACH study (2015)</td>
<td>Higher Rutherford category, diabetes,* non-ambulatory,* infrapopliteal arterial lesion, regular dialysis,* impaired pressure sensation</td>
</tr>
</tbody>
</table>

*Data from multivariate analysis. CLI, critical limb ischemia; non-claudicant CLI, CLI patients without preceding intermittent claudication; higher Rutherford category, tissue loss rather than rest pain.

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Department of Vascular Surgery, Asahikawa Medical University, Asahikawa, Japan

Mailing address: Nobuyoshi Azuma, MD, PhD, Department of Vascular Surgery, Asahikawa Medical University, 2-1 Midorigaoka-higashi, Asahikawa 078-8510, Japan. E-mail: nazuma@asahikawa-med.ac.jp


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Regarding the clinical features of CLI patients without preceding claudication, Shirasu et al reveal that diabetes, low albumin concentration and being non-ambulatory are systemic factors for CSLI. They also report that CSLI patients likely develop tissue loss rather than rest pain at presentation, and the arterial lesions are located more distally compared with CLI patients with preceding claudication. Takahara et al reported similar clinical features of CSLI patients, and they also found that chronic kidney disease (CKD) on regular dialysis is a significant factor for CSLI.

Determining these clinical features is very important for exploring the reasons why patients do not feel the walking pain in the severe ischemic condition. Regarding the pathophysiology and the reasons why patients do not experience claudication before the onset of CLI, Mätzke et al proposed 3 hypotheses: (1) CSLI patients move very little or not at all in their daily lives, which is not sufficient to develop symptoms; (2) sensory loss in their legs prevents perception of the symptoms; and (3) the lack of symptoms is related to localization of the occlusive lesions in the arterial tree. All significant factors demonstrated by Shirasu et al seem to be reasonable for explaining these 3 hypotheses. Furthermore, Takahara et al clearly demonstrated that CKD on dialysis contributes to the development of infrapopliteal arterial lesions that in turn develop into CLI without preceding claudication. These findings suggest that the increasing numbers of CSLI patients in Japan can be explained by demographic changes, including increasing diabetes and diabetic CKD populations in the aging society.

Shirasu et al also reveal the prognosis of CLI patients without preceding claudication, and this is the most important aspect of their report. The prognosis of CSLI has not been thoroughly researched. White et al reported favorable prognosis in CSLI patients, whereas the TASCII Working Group described that excess mortality and amputation are expected in CSLI. Shirasu et al demonstrate that the ischemic stage at presentation of CLI patients without preceding claudication was already much more severe and that their amputation-free survival after revascularization was also worse compared with CLI patients with preceding claudication. The differences between these patient groups in terms of their prognosis can be partially explained by differences in their background disease. However, another reason for the poor prognosis may be explained by the reduced chance of receiving medical interventions because of the loss of the signs of existing PAD. The intermittent claudication can be an important alerting sign to encourage patients to visit hospital. Therefore, CSLI patients may reduce their chance of receiving intensive medical care through risk factor modification as well as the taking of antiplatelet drugs or statins.

If CSLI patients have a poor prognosis as Shirasu et al report, vascular specialists as well as family physicians should recognize that patients with very poor prognosis exist among the asymptomatic PAD patients whose legs are generally thought to have benign prognosis. In other words, there is substantial heterogeneity in terms of the prognosis of the asymptomatic PAD population (Figure). Furthermore, the numbers of these CSLI patients continue to increase in accordance with increasing numbers of diabetic patients and CKD patients in the aging society. Both vascular specialists and family physicians need to consider how to diagnose CSLI patients among the asymptomatic PAD patient population before the condition progresses.

**Figure.** Conceptual natural history of patients with asymptomatic peripheral arterial disease (PAD). The asymptomatic PAD patient population is substantially heterogeneous, although their prognoses have not been thoroughly studied. Most CSLI will deteriorate to R5 or R6 directly by a minor trauma via pathway “c”. The number of patients with CLI progressing through pathways “c” and “b” may be nearly equal to or exceed those with CLI progressing through pathway “a” in the current situation in Japan. CSLI, chronic subclinical limb ischemia; CLI, critical limb ischemia; R4, R5, R6, Rutherford categories 4, 5, 6.
deteriorates into the highest Fontaine classification. If CSLI patients can be identified before the onset of CLI, they can benefit from medical interventions such as risk reduction strategies and preventive foot care.

Shirasu et al conclude that further prospective longitudinal studies are necessary. Currently, a prospective multicenter observational CLI study named SPINACH is ongoing in Japan. Japan is one of the most advanced countries in terms of the diabetic and dialysis-dependent population, as well as the aging population, which means that Japan may be the most advanced country for CSLI patients. The SPINACH study is now prospectively following 559 CLI patients, including 281 CLI patients without preceding claudication. Therefore, the study will confirm whether CLI patients without preceding claudication have a poor prognosis and explore the factors that contribute to that poor prognosis.

References