To the Editor: Ischemic peripheral neuropathy is a term used to describe the neurological deficits of peripheral nerves in patients with peripheral artery obstructive disease (1). Although ischemic peripheral neuropathy is a major complication of critical limb ischemia resulting in impaired quality of life, effective treatment for ischemic neuropathy is not available at present.

Recently, it has been reported that therapeutic angiogenesis using vascular endothelial growth factor (VEGF) gene transfer for critical limb ischemia improves ischemic neuropathy in animals (2) and humans (3). We reported that therapeutic angiogenesis using autologous transplantation of bone marrow mononuclear cells (BM-MNCs) for peripheral artery disease increased limb perfusion and improved clinical conditions, such as ischemic pain, claudication, and ischemic ulcer (4,5). Therefore, we examined whether autologous transplantation of BM-MNCs would improve ischemic neuropathy with critical limb ischemia in humans.

We enrolled 14 patients with angiographically-proven critical limb ischemia (Table 1). In each patient, autologous transplantation of BM-MNCs (4.89 ± 5.21 × 10^6 cells) was performed in 1 ischemic leg (treated limb), and saline was injected into another leg (control limb). Before and 1 month after transplantation, we examined subjective symptoms (visual analogue scale as an index of rest pain severity, pain-free walking distance), ankle brachial pressure index, and digital subtraction angiography score. Tibial motor nerve conduction velocity (MNCV), sural sensory nerve conduction velocity (SNCV), compound muscle action potential (CMAP), tibial and sural sensory nerve action potential (SNAP), and quantitative vibration threshold time (QVT) were recorded. We also measured MNCV, SNCV, CMAP, and SNAP of 23 age- and sex-similar healthy subjects. This study was blinded to the investigator who assessed nerve functions. The protocol was approved by the institutional ethics committee of Kurume University. Written informed consent was obtained from all subjects.

Treatment significantly improved subjective symptoms and peripheral blood perfusion only in the treated limb (Table 1). The MNCV and CMAP could be measured in the treated limb of all patients, and in the control limb of 12 patients. Before treatment, both MNCV and CMAP were significantly smaller in the treated limb than in the healthy group (Table 1). Treatment significantly increased both MNCV and CMAP only in the treated limb. Treatment recovered MNCV and CMAP to the level of the healthy group. The QVT was significantly improved only in the treated limb, but not in the control limb after treatment (Table 1). The SNCV and SNAP of the patients did not differ from those of the healthy group, and the treatment did not affect them (Table 1).

The major findings of this study are as follows. First, autologous BM-MNC transplantation improved subjective ischemic and neuropathic symptoms in patients with critical limb ischemia. Second, the treatment improved not only peripheral blood perfusion but also peripheral nerve function. This study confirmed our previous findings (4,5) that autologous BM-MNC transplantation improved ankle brachial pressure index, digital subtraction angiography score, and subjective symptoms in treated limbs. Furthermore, BM-MNC transplantation improved objective peripheral nerve functions (MNCV, CMAP, and QVT) in the treated limb but not in the control limb, suggesting that the effects were not related to natural course or nonspecific effects. Thus, autologous BM-MNC transplantation might improve not only peripheral blood perfusion but also ischemic peripheral neuropathy.

The improvement of peripheral nerve function may be caused by better blood perfusion after autologous BM-MNC transplantation. Simovic et al. (3) reported that VEGF gene transfer improved the neuropathic symptoms, CMAP, and QVT. They speculated that the mechanisms of the nerve function improvement were related to the size of the vessels restored by VEGF. In fact, angiogenic cytokine-induced neovascularization principally involves the small vessels including the vasa nervorum (<180 μm), the nutrient vessels of peripheral nerves. Thus, transplanted BM-MNCs might have improved nerve perfusion and function directly by contributing to neovascularization, and indirectly by secreting a variety of angiogenic cytokines. In addition, because transplanted BM-MNCs presumably contain various kinds of cells, such as bone marrow stromal cells, BM-MNC transplantation might have regenerated the damaged peripheral motor nerve.

This study has limitations. This study was an observational open-label study with no placebo control group. In addition, the number of patients enrolled in this study was small, and the duration of the follow-up was short.

Ken Arima, MD
Yousuke Katsuda, MD, PhD
Division of Cardio-Vascular Medicine
Department of Medicine
Kurume University School of Medicine,
67 Asahi-Machi
Kurume, Fukuoka 830-0011 Japan
E-mail: katsuda@med.kurume-u.ac.jp

Yoshiaki Takeshita, MD, PhD
Yutaka Saito, MD, PhD
Yasuyuki Toyama, MD
Yoshio Katsuki, MD
Masanori Ootsuka, MD
Hiroshi Koiwaya, MD
Ken-ichiro Sasaki, MD, PhD
Hisashi Kai, MD, PhD
Tsutomu Imaizumi, MD, PhD

doi:10.1016/j.jacc.2010.02.050
Coronary Slow-Flow Phenomenon or Syndrome Y

A Microvascular Angina Awaiting Recognition

Dr. Cannon is to be complimented on his important contributions in the description of the elusive pathophysiology of microvascular angina. We would like to contribute to his otherwise excellent review (1) recently published in the *Journal* by making mention of another condition that also depends on an impairment in the regulation of coronary microvascular resistances and that, therefore, should be included among the “microvascular angina” synonyms. This condition, known as the coronary slow-flow phenomenon (CSFP), is increasingly recognized as a separate clinical entity along with the “classic” coronary syndrome X based on 3 degrees of evidence: 1) the coronary syndrome X and the CSFP differ mechanistically; 2) the CSFP has typical clinical features that differ strikingly from those of coronary syndrome X; and, finally, 3) its prognosis is not as benign as that traditionally described for coronary syndrome X.

Although a number of formal definitions have been proposed, the CSFP essentially consists of a delay in the progression of the contrast injected in the coronary vasculature during coronary angiography. Importantly, invasive studies have demonstrated that, compatible with the delayed opacification, resting coronary artery resistances are abnormally elevated in these patients; in striking contrast with “classic” coronary syndrome X, however, these