growth factors for inducing angiogenesis. In this study, both the angiogenic growth factors were higher after BMCI treatment than after the injection of PBS alone. We assumed that the production of multiple angiogenic growth factors and the endothelial differentiation from these implanted bone marrow cells accelerated the development of microvessels, resulting in the enhanced regional blood flow. We also considered that the enhanced cardiac function after BMCI treatment mainly contributed to the increased blood flow in the LV anterior wall. Although previous studies found that cardiomyocytes were differentiated from bone marrow stem cells [19, 20], this differentiation would be insufficient to affect any increase in cardiac function.

According to past reports, impaired cardiac function can be improved by the implantation of bone marrow cells cultured with 5-azacytidine, but not by that of fresh bone marrow cells, although the implantation of fresh bone marrow cells induces angiogenesis [21]. These conflicting results could be related to differences in the experimental design or implanted cell number.

In conclusion, the implantation of autologous bone marrow cells is an effective method of inducing therapeutic angiogenesis in ischemic heart disease. BMCI is a simple treatment and easy to perform in clinical trials compared with other methods such as the direct injection or the gene transfer of angiogenic cytokines [22, 23].

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INVITED COMMENTARY

The study by Nishida and colleagues complements other studies published by this group and that of other groups which have examined the effects of implantation of bone marrow cells into the ischemic myocardium or ischemic hind limb of rats. The distinguishing aspect of the present study is that a novel method was used to create ischemic but not infarcted tissue. The authors used a thin copper wire as a guide to place a ligature around the left

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anterior descending coronary artery. The authors contend that this produced a stenotic but open vessel.

Most prior studies in rodent models of ischemia have simply ligated the left anterior descending coronary artery with a suture and the authors have acknowledged the limitation of having an acute MI versus chronically ischemic tissue. Larger animal models of chronic myocardial ischemia used to investigate angiogenesis, improved myocardial performance, or basic physiology of the collateralized myocardium have significant advantages. The two more popular of these methods are the ameroid occluder model and the repetitive embolization model of chronic ischemia, often adapted in the pig, dog, or pony. The ameroid occluder is a hydrophilic casein plastic (ameroid) encased into a stainless steel or hard plastic ring. As the center portion collects water, it occludes the vessel, usually over 10–20 days. The repetitive embolization model uses an injection of microspheres or similar small particles into the coronary artery. Both models have advantages and disadvantages. However, the use of large animal models is very expensive and time consuming.

If the authors have, in fact, developed a new rodent model of chronic myocardial ischemia, this could have a major impact on the progress of future work. However, the authors have not directly assessed whether the artery remains open after the ligature is placed or on the state of the artery after 60 days when flow measurements are made. Whereas, the anterior wall of the hearts was hypokinetic and not dyskinetic according to the authors, my impression is that many or most of these arteries had occluded within days after placement of the ligature. Further studies will be required to verify the model.

The use of bone marrow, skeletal myocytes, and other transplanted cells to improve vascular density and myocardial perfusion and function is still somewhat novel in practice but not novel in concept. In deed, Philippe Menasche has even transplanted skeletal myoblasts into the hearts of patients. This is a long jump from rat research. However, to date, the results have been modest and many obstacles must be overcome before cell-based therapy will be in widespread clinical practice. Despite these issues, the authors have nicely demonstrated increased end-systolic dimension and improved factional shortening, increased vascular density, blood flow, and left ventricular thickness in rats having received the bone marrow implantation. They should be congratulated on their work. However, before dramatic conclusions can be drawn from animal experiments, they need to be repeated in a large animal model of chronic myocardial ischemia. Better yet, positive results need to be demonstrated in patients before cell-based therapy is expanded to patient care.

Frank W. Sellke, MD

Division of Cardiothoracic Surgery
Beth Israel Deaconess Medical Center
Harvard Medical School
110 Francis St, No. LMOB Suite 2A
Boston, MA 02215
e-mail: fsellke@caregroup.harvard.edu