Mending the Broken Heart

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There is now indisputable evidence that an elevated white count predicts an adverse prognosis in acute myocardial infarction.1, 2 Although a cause and effect relationship is not established, several authors have speculated that an activated inflammatory state could predispose to cardiac rupture or destabilize nonculprit unstable plaques in the coronary system. Thus the report by Tomoda and Aoki in this issue of Clinical Cardiology,3 showing that an elevated level of circulating bone marrow stem cells predicts an improved ejection fraction at 6 months post infarction, serves as a challenge to existing dogma. Is it possible that an increased white count reflects the magnitude of injury, and that the cells are performing a beneficial function? To deal with this possibility, we need to examine the mechanism responsible for the entry of bone marrow stem cells into the circulation after myocardial infarction.

In bone marrow transplantation therapy, homing refers to the phenomenon by which intravenous stem cells specifically engraft in the bone marrow and not in other organs. Homing of bone marrow stem cells is now also thought to occur following various types of tissue injury. In patients with myocardial infarction, both circulating CD34+ mononuclear cell counts and plasma levels of vascular endothelial growth factor are significantly increased, peaking on Day 7 after onset.4 Although the mechanism is still being defined, recent data suggest that stem cells mobilization is induced by granulocyte stimulating factor (GCSF) and other cytokines. Both in the marrow and at the target site, mobilization and migration of stem cells are facilitated by upregulation of extracellular matrix proteins and proteolytic enzymes. After the cells enter the circulating blood, locally expressed adhesion molecules mediate their attachment driven by a gradient of chemoattractants. At the injury site, the stem cells either differentiate or fuse with existing tissue cells through poorly defined mechanisms involving both cell-to-cell contact and growth factors.5, 6

The critical importance of the report of Tomoda and Aoki, therefore, is that it fits with the new idea that stem cell repair of cardiac and vascular tissue is a naturally occurring process after injury.7, 8 This new concept has led to new therapeutic strategies that aim to recapitulate and amplify the natural process. After stem cell injection directly into the myocardium of animals with infarction, our laboratory and a number of others have reported that labeled stem cells develop the phenotypic characteristics of myocytes and endothelial cells and express myocyte-specific and endothelium-specific proteins.9–13 Quantitative measurements show that infarct size is smaller, accompanied by both improved myocardial perfusion and function. Collateral flow at rest and during adenosine stress increases, accompanied by as much as a 50% increase in regional myocardial wall thickening during stress.10

Based on these reports, we might speculate that similar results could be obtained by using the intrinsic reparative mechanisms of either homing or mobilization. These approaches have also been successful in animal laboratory studies. Stem cells injected intravenously do home to injured myocardium. After intravenous injection of stem cells in the murine infarct model, the percentage of myocardium infarcted was reduced from 36 to 12%, capillary formation was threefold greater, and the number of apoptotic cells was reduced sixfold at 15 weeks.14 Other studies suggest that stimulation of mobilization by GCSF or other cytokines is sufficient to produce the same effect on cardiac function and perfusion in the murine infarct model.15, 16 Cytokine-induced cardiac repair had has been shown to decrease mortality by 68%, infarct size by 40%, and left ventricular end-diastolic volume by 26%.

Clinical experience using these new ideas is just beginning. Strauer et al. published the first report on the safety of intracoronary autologous bone marrow cells injection in 10 patients.17 At 5 to 9 days after acute myocardial infarction, high-pressure infusions of 2–3 ml of the patient’s own bone marrow cells in suspension were delivered directly into the culprit vessel during 2 to 3 min balloon occlusion. The treated group was

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compared with 10 patients who refused cell therapy. At 3 months, the control patients exhibited no statistically significant change in cardiac function or perfusion, whereas the treated group had a reduction in their segmental wall motion defect from 30 to 12%, and a reduction in infarct region, as determined by 201thallium perfusion defect, from 174 to 128 cm². Although stroke volume increased significantly, ejection fraction remained unchanged. The authors reported that no side effects were observed at any point in time.

A second trial, the TOPCARE-AMI (Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction) study, is comparing the effect of intra-coronary injection of circulating endothelial cells (EPCs) to bone marrow cells (BMCs) in patients with reperfused acute myocardial infarction. Of the first 20 patients, 11 received EPCs and 9 received BMCs. At 4 months, left ventricular ejection fraction had improved by 9.5% in patients injected with either EPC or BMC, compared with rates of 3.5% seen in historical controls. Coronary flow reserve measured by stress echo was improved in both the target and reference vessels of both patient groups. As with the report by Strauer et al., no adverse events were reported, and the injection of cells was not accompanied by an increase in cardiac enzymes.

Finally, a number of trials of transcendocardial injection of commercially produced mesenchymal stem cells or freshly aspirated bone marrow cells are now underway. Injection is controlled by left ventricular electromechanical mapping technology in the catheterization laboratory. Early experience suggests that this approach is also technically feasible and can be performed safely. All the clinical studies, of course, are too preliminary to establish efficacy, but it seems reasonable to conclude that they do establish short-term safety. Clearly, the final arbiter of the effectiveness of stem cell therapy in the management of acute and chronic myocardial infarction must be randomized clinical trials that assess the balance between likely benefit and theoretical risk.

References

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