Editorial

Optimizing cardiac cell therapy: From processing to delivery

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In this issue, McConnell and colleagues report a detailed examination of the impact of autologous skeletal myoblast transplantation in a chronic ischemic cardiomyopathy model in sheep. They injected the cells prepared by GenVec, Inc, at multiple sites in the infarct zone. They concluded that cardiac contractility was not improved, but cell implantation prevented ventricular dilation. The study highlights several important issues in cardiac cell therapy and its future in clinical application.

Most preclinical reports have demonstrated improvement in systolic and diastolic properties after cell transplantation. According to McConnell and colleagues, however, the predominant impact of myoblast implantation was not on systolic function. Their finding could be related to the data analysis. For example, a significant enhancement of cardiac performance might have been detected if they had made pressure and volume measurements at lower volumes and if they had performed a more robust statistical analysis (an analysis of covariance).

In this study, McConnell and colleagues reported at 6 weeks a 21% reduction in end-systolic volume index (ESVI) in cell-transplanted sheep relative to control sheep (98 ± 18 mL/m² vs 124 ± 15 mL/m²), consistent with observations by other investigators. Increased ESVI, independent of ejection fraction, has been associated with a marked increase in mortality in patients after myocardial infarction. In patients undergoing surgical ventricular restoration for dilated ischemic cardiomyopathy, a preoperative ESVI lower than 80 mL/m² is associated with a 16% lower mortality than is an ESVI greater than 120 mL/m² (P < .001). Cardiac cell therapy may therefore improve survival for patients not eligible for surgical revascularization and ventricular remodeling by preventing progressive ventricular dilation.

McConnell and colleagues injected cryopreserved myoblasts. Cryopreservation will extend the time available to harvest, process, and prepare the cells for implantation. The cryopreserved cells may also be stored, thus increasing the flexibility of timing of cell transplantation. In addition, some cells can be implanted, and the remainder can be cryopreserved for repeated implantation in the future. Cell cryopreservation may broaden the clinical applicability of cell transplantation.

On the other hand, the outcome of cardiac cell therapy is determined by the number, vigor, and viability of injected cells. More advanced cell passages, abnormal cell morphology combined with cryopreservation, negatively affect cell growth and vigor. In addition, recent evidence suggests that the proportion of injected cells surviving to engraft in the infarcted myocardium is low, and cryopreservation may have contributed to the less impressive functional improvement found in this study. The cells may leak out of the injected region and may be carried to other organs, contributing to the rapid cell loss seen in the first 24 hours. Acute oxidative stress, ongoing ischemia, and inflammation also reduce cell survival. In the report of

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McConnell and colleagues,\textsuperscript{1} the low myoblast survival despite a high viability may have limited the beneficial impact of cell transplantation.

To improve survival and engraftment of the transplanted cells, many investigators have combined cell transplantation with protein or gene therapy. Injection of fibroblast growth factor or vascular endothelial growth factor before cell transplantation improved cell survival in infarcted myocardium.\textsuperscript{10,11} Insulin growth factor 1 transfection (Figure 1), heat shock preconditioning, and antiapoptotic treatment of donor cells also augmented the benefits of cell transplantation.\textsuperscript{12,13} Genetic enhancement of donor cells before cryopreservation and growth factor enrichment of recipient myocardium before cell delivery may improve the functional benefit by enhancing cell survival.

As the report by McConnell and colleagues\textsuperscript{1} illustrates, several aspects of cardiac cell therapy still require clarification, including the optimal cell processing and delivery techniques, the best timing of cell implantation, and the protein or gene enhancements that will significantly improve cell survival. Large animal investigations, such as this report by McConnell and colleagues,\textsuperscript{1} are essential to guide future clinical trial design and determine the appropriate role of cardiac cell therapy in the treatment of ischemic heart disease.

References


