Cellular cardiomyoplasty for myocardial support and regeneration

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Myokardiale Unterstützung und Regeneration durch zelluläre Kardiomyoplastie


Schlüsselwörter: zelluläre Kardiomyoplastie, Herzinsuffizienz, Stammzellen.

Summary. Background: Cell-based regenerative therapy is undergoing different experimental and clinical trials in order to limit the consequences of decreased contractile function and compliance of damaged ventricles following myocardial infarction.

Methods: An overview of the actual status quo.

Results: Over 200 patients have been treated worldwide with cell-based procedures for myocardial regeneration. Results are preliminary.

Conclusions: Cellular cardiomyoplasty seems to reduce the size and fibrosis of infarct scars, limit postischemic remodelling, and restore regional myocardial contractility.

Key words: cellular cardiomyoplasty, myocardial regeneration, heart failure, cellular biology.

The recent progress in cellular and molecular biology has made possible the development of new therapies for heart failure. One of the most innovative consists of the transplantation of autologous expanded cells into the myocardium for heart muscle regeneration. This approach is called cellular cardiomyoplasty. The adult myocardium cannot effectively repair after infarction due to the limited number of stem cells. Thus, most of the injury is irreversible. For this reason, cell transplantation strategies for heart failure have been designed to replace damaged cells with cells that can perform cardiac work, either in ischemic or idiopathic cardiomyopathies [1, 2].

Grafting of healthy cells into the diseased myocardium holds enormous potential as an approach to cardiovascular pathology. Cellular cardiomyoplasty (CMP) consists of cell implantation to implement the growth of new muscle fibers and to develop angiogenesis in the damaged myocardium that potentially may contribute towards improving systolic and diastolic ventricular functions and reversing the postischemic remodeling process [3–6].

Current clinical possibilities in cell therapy for heart failure are the transplantation into the damaged myocardium of different types of cells such as autologous myoblasts (originating from skeletal muscle) (Fig. 1), bone marrow stem cells, peripheral blood stem cells, smooth muscle cells, angioblasts and endothelial cells [7–11].

While various donor cells have been studied to induce myogenesis after myocardial infarction, recent interest has arisen in promoting cardiac angiogenesis. These techniques retain an important potential as an adjunct to myogenic cellular transplantation in inducing angiogenesis in the injured myocardium, because skeletal myoblast mortality after implantation in the highly fibrotic infarcted myocardium seems to be high since the oxygen and nutrients supplies are limited within the scar.

Indications

Ischemic cardiomyopathy

Clinical application for cell transplantation should be in patients presenting a cardiac dysfunction due to an extensive myocardial infarction, without possibilities of surgical or percutaneous revascularization. The objective of cellular CMP is to limit infarct expansion and cardiac remodelling, and regenerate the myocardium. Patients
with left and/or right ventricular myocardial infarction and with ischemic mitral valve regurgitation can be included.

**Idiopathic dilated cardiomyopathy**

Nonischemic cardiomyopathy is also a major cause of heart failure, with high mortality rates. Cell transplantation could offer new hopes for this disease by restoring impaired heart function. Cellular CMP may improve heart function in patients with dilated cardiomyopathy, since the grafted cells appear to survive better in the host myocardium because myocardial irritation in this pathology is not significantly impaired.

**Mechanisms of action**

The many proposed mechanisms of action in cellular CMP are reduction of the size of infarct scars, limitation of postischemic ventricular remodeling, improvement of ventricular wall thickening and compliance, and increase of regional myocardial contractility. When skeletal myoblasts are used for cellular CMP, the sequence of actions seems to be the following: cells transplanted into the myocardium first impact on diastolic dysfunction, and subsequently, when sufficiently organized in myotubes and myofibres, systolic performance improves [1, 7, 11].

The technical approach used to implant the cells should influence the efficacy of cellular CMP. Cell mortality after transplantation seems to be important when they are grafted in the center of highly fibrotic ischemic scars, since the supply of oxygen and nutrients to the chronic ischemic myocardium is greatly limited. Implantaing the cells mainly in the peri-infarct areas may improve the rate of surviving cells, thus the size of the infarct scar undergoes a centripetal reduction.

It is possible that periodically repeated cell injections are necessary to progressively reduce the infarct scars in ischemic cardiomyopathies or to gradually improve the diseased myocardium in nonischemic cardiomyopathies. This approach should be facilitated by the development of percutaneous catheter-based cell implantation procedures.

**Research and development**

The following studies have been performed in our institution.

**In vitro stem cell electrostimulation for myogenic preconditioning**

Ex vivo cell electrostimulation was applied by our group in the driving process of conditioning bone marrow stem cells towards cardiac-type myogenic cells. In vitro electrostimulation of human bone marrow cell cultures for myogenic preconditioning has been performed using a bipolar system including an external pacemaker and specific electrodes, submerged into the culture medium. After 3 weeks we observed an increase in cell multiplication, improved cells organization (electrically oriented myotubes), and myogenic differentiation (Fig. 2). Since stem cells can differentiate into fibroblasts after implantation in myocardial scars, this method should be proposed to precondition cells before implantation.

**Electrostimulated “dynamic” cellular cardiomyoplasty**

Atrial synchronized biventricular pacing is indicated in many heart failure patients to correct conduction disorders associated with chronic systolic and diastolic dysfunction. Electrostimulation associated with cellular CMP was proposed by our group to transform passive cell therapy into “dynamic cellular support”. The principles of electrophysiological conditioning of muscle fibres (e.g. dynamic CMP) were applied by our group in cellular CMP since skeletal myofibres express predominantly fatigue-sensitive fast myosin, which is not suitable for cardiac work. Electrostimulation of the ventricles following skeletal myoblast implantation induced the contraction of the transplanted cells and a higher expression of slow myosin, better adapted for chronic ventricular assistance [12, 13].

**Autologous human serum for cell culture**

Traditional cell culture techniques involve the use of fetal bovine serum for cell growth. Contact of human cells with fetal bovine serum results after 3 weeks in fixation of animal proteins on the cell surface, representing an antigenic substrate for immunological and inflammatory adverse events. After cell implantation into the heart an inflammatory reaction can occur with subsequent fibrosis, representing a risk for micro-reentry circuits that can generate ectopic ventricular arrhythmias. Thus, di-

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Fig. 1. Human skeletal myoblasts isolated from a muscle biopsy. After 3 weeks in culture, medium myoblasts are recognized by desmin antibodies (lower panel)