Gene Therapy and Cardiomyocyte Transplant in Heart Failure

Mircea CINTEZA\textsuperscript{a,b}

\textsuperscript{a}“Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania
\textsuperscript{b}Emergency University Hospital of Bucharest, Romania

Since decades, prognosis in advanced heart failure is considered as bad as in cancer.

One reason is that two or three decades before cancer was considered incurable. Now there are curable cancers, but a lot of incurable as well. Today congestive heart failure rested incurable almost in the totality of cases. We may try to treat the cause, like ischemia, but if heart failure is installed, the force of the ventricle will not be restored. We may use good drugs or devices, but it is just a physiopathological approach. The real mechanism by which heart myofibrils lose their inotropism is not well understood and, consequently, not treated.

But a new therapeutic era for heart failure seems to be ready to be applied in humans: gene therapy, with action on potential subcellular targets to improve contractility of existing myofibrils (1-3) or cardiomyocyte transplant (4-6). Both ways have large studies on animals, but there are clinical studies on humans as well (3,6).

For the experiments to manipulate subcellular components of the exiting failing myofibrils some problems are common. First, it is important to find a safe but efficient vector to transfer the genetic material which will act to change the bad effectors. To date, modified viruses seem to be the most efficient vectors and their injection can be performed either directly into the myocardium and by the intracoronary way. The second problem is that the transformed cells should deliver new healthy proteins on a long term. In this type of experiments the new Deoxyribonucleic acid (DNA) is implanted into the somatic cells, so they act only on the individual to whom they were injected. There are other experiments in which the vectors replace genes into germ cells, so the new information will be transmitted to the next generations. This type of experiments is much more complicated and, if applied on humans, necessitate much more drastic ethic legislation.

Coming back, the transformed somatic cells are sometimes recognized as non self by the host.

Address for correspondence:
Mircea Cintzea, Department of Cardiology and Internal Medicine, Emergency University Hospital, 169 Splaiul Independentei, 5th District, 050098, Bucharest, Romania.
E-mail: mirceacintzea@yahoo.com

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immune system. After a shorter or longer period of activity, they will be eliminated and the correction of the anomaly will disappear (1).

In experimental models, in the failing heart the cardiomyocytes have impaired function both in systole and in diastole, due to an abnormal calcium homeostasis. As a consequence of the reduced activity of the sarcoplasmic reticulum calcium ATPase pump (SERCA2a) there will be a reduced rate of calcium removal and, consequently, a larger quantity of calcium in diastole (1). The reduced activity of SERCA2a is typical for heart failure and is partly due to the presence, in a heart failure status, of a larger amount of phospholamban, a SERCA2a inhibitor.

The experimental works for restore of calcium homeostasis by genetic means recovered the activity of SERCA2a either directly or by decreasing the activity of phospholamban. The viral vector acting on the DNA either increased the expression of SERCA2a or decreased the expression of phospholamban (1,2). As a consequence, the energetics of the myofibrils increased, the diastolic calcium decreased and even the survival of the animals was improved.

What is important is that we have already clinical trials on humans and some results are already published: the CUPID Study (3). 39 patients received intracoronary adeno-associated virus type 1/sarcoplasmic reticulum Ca(2+)-ATPase or placebo. At 6 months the treated group demonstrated improvement or stabilization both in clinical, as well in more objective parameters: the New York Heart Association Class, the Minnesota Living With Heart Failure Questionnaire, the 6-minute walk test, the peak maximum oxygen consumption, N-terminal pro-hormone brain natriuretic peptide levels, and left ventricular end-systolic volume. 6 significant side effects were noted. At 12 months a significant decrease in cardiovascular events was observed (3). New clinical studies are necessary to confirm this way of therapy for severe heart failure.

Other gene therapies at the molecular level have outstanding results in experimental studies. Beta receptors are reduced in heart failure. Injection of the beta-2 adrenergic receptor gene increased its expression 10 fold after 3 days and contractility increased. Other observation showed that the 60 fold increase improves contractility, but a 100 fold increase produces fibrosis (1). Other manipulations with positive results in experiments act on adenylyl cyclase (animals not only had better contractility, but also had improved survival), or on V2 vasopressin receptor (1). Time came to begin larger studies on humans.

Another approach with many clinical studies is the transplant of cells in the failing myocardium (4-6). There are different results and inconsistency in repeating good experiments. The main problems with cellular transplant in the failing myocardium are:
- The source and type of transplanted cells
- The way to make them seed
- The way to transform them properly into cardiomyocytes accepted by the host
- The way to make cardiomyocytes contract properly
- The way to develop locally angiogenesis
- The way to make the new cardiomyocytes to survive and work properly on a long term

It seems that there is place for improvement in any of the mentioned points of the transplant process.

Cells utilized to day as a source to be transplanted in the myocardium are various:
- Neonatal cardiomyocytes
- Skeletal myoblasts
- Hematopoietic stem cells
- Marrow mesenchymal stem cells
- Skeletal muscle myocytes
- Umbilical chord cells

These cells are implanted in the failing myocardium in dilated cardiomyopathy or even at the periphery of an infarction scar. There after most of them are manipulated to turn into cardiomyocytes and begin to contract (4-6).

Another very important approach is to make the implanted cells to influence, improve or transform the local cells into competent cardiomyocytes (1). Some researchers consider that these new cells work most often by paracrine means and not transforming themselves into contracting cardiomyocytes. They release growth factors, cytokines and others which act on the local cells. There are even proves that fibroblasts in the post myocardial infarction scar may be transformed in that way into cardiomyocytes (1).

In experimental models on animals results were almost always positive regarding improvement of contractility. Human studies gave various results. The effect on the contractile function of the patients was generally positive, but
the effect on major cardiovascular endpoints was inconclusive. Clinical studies like BOOST, REPAIR AMI, ASTAMI and others did not bring to patients major clinical benefits.

However, a meta-analysis in 2012 (6) on 2625 patients in 50 studies (an important figure for human studies) gave a more optimistic conclusion. It confirmed that overall local benefit was significant (Ejection Fraction – EF - increased by 3.96 % for a period of at least 2 years in patients with or without myocardial infarction; when present, infarct size was reduced by more than 4%). All-cause mortality, cardiac mortality and recurrence of the myocardial infarction were better in the treated groups, but not with large differences. This meta-analysis is an important positive step for the continuation of clinical studies in the field.

Two studies published after the meta-analysis, (TIME, n=120 and SWISS AMI, n=200) gave inconclusive results as well (1). An interesting clinical trial published recently (MAGIC, n=27) demonstrated an important increase in EF (from 48.7 to 55.1%) in the group where the granulocyte-colony stimulating factor (G-CSF) was used to mobilize the injected stem cells (1). However, stent thrombosis was more frequent in the treated patients. This brought supplementary arguments for the paracrine action during the cell transplant in the failing myocardium.

In 2005 Popescu LM, Hinescu ME and others described a new type of cells present in many tissues, later called telocytes (7). Their body is about 0.5 micron large, but they have telopodes long of several hundreds of microns. These cells make an important network at the periphery of functional cells in many tissues (pancreas, colon, lung, skin, ovary etc.), but the network is very important in the myocardium. Its role seems to be to integrate information on the tissue structure (8).

After a myocardial infarction, about 1000 genes are activated in the telocytes along the repairing process. Researchers consider that transplanted cells in the myocardium cannot plenty develop because of the lack of the integrative network given by telocytes. Adding telocytes in the transplant process could bring the missing point to a definitely better clinical result (8).

To conclude, both ways to repair failing myocardium have important positive results in humans. The failing myocardium, be it after infarction, with scar or in a dilated cardiomyopathy of different origins was considered until recently a final tissue without the possibility of recovery. Both gene therapy on the subcellular targets and cardiomyocyte transplant show that the repair is consistently possible.

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REFERENCES