

Can Myocardium Regenerate?

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The official answer is NO (1).

However, there are a lot of arguments that a small “yes” answer does exist today – the myocardium can regenerate a little bit (2). And there is hope that genetic engineering in medicine will boost this answer, turning it into a big “YES”, in order to repair the damaged myocardium instead of merely helping the resting one by drugs or mechanically.

How does the heart grow?

Before birth, myocardial cells proliferate and constitute the embryonic heart. Soon after birth,

the heart stops proliferation and becomes a “post-mitotic” organ (1, 2). The 10-fold growth of the heart, from the dimensions of a newborn’s heart to those of an adult’s one, is done by hypertrophy only. Later on, if the adult makes heavy exercise, the heart becomes an “athletic” heart also solely by hypertrophy. There are very few exceptions to this concept, without clinical relevance.

Can we inseminate stem cells into the myocardium?

The answer is “Yes, of course”. The problem is that there are already tens of clinical studies with very little increase in left ventricular function and no significant effect on clinical income in patients with heart failure (3).

The main problems with cell insemination into the myocardium are (4, 5):

- the source and type of implanted cells;
- the way to transform them into functional myocytes;
- the way to develop new angiogenesis, in order to make a new region of functional myocardial tissue.

The source of cells is very important and there are a lot of possible alternatives. Hemato-

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Article received on the 28th of June 2020 and accepted for publication on the 29th of June 2020

poietic cells, induced pluripotent stem cells, myocardial stem cells and even skeletal muscular stem cells have been used (5). Each of these and some others had some success in becoming functional new myocytes.

The way to prepare the source cells to be in-seminated is also very important and various modalities were tried: non-genetic ones (drugs, cytokines, hypoxia), genetic engineering (DNA, RNA), paracrine interventions (5). In this respect, attempts have been made to take into account the use of telocytes. These cells are present in the interstitium of the myocardium, have very, very long and thin extensions which constitute a real network in the myocardial tissue and are considered to play a role in the nutrition and functioning of the myocytes (6)

As previously mentioned, there are already tens of clinical studies on hundreds of patients followed for several years (3). The results were not so impressive and a new idea emerged: instead of implanting cells, to implant pieces of tissue constructed *in vitro*, with cells and nutrient fluids fixed on the scallop before the tissue is fixed into the myocardium. This procedure is called 3D bio printing (7, 8).

Can we fix artificial tissue into the myocardium?

This 3D bio printing method implies three phases: creation of the scallop, preparing the “bio ink” and constructing the tissue.

The scallop is done by biological or artificial fibres put into a 3D construction. The main problem is that the vessel network has to be thin enough to develop neovascularisation. At present, the best diameter of the vessels inside the scaffold is about 20 microns and, with endothelial cells injected inside, this scaffold is capable to generate new micro vessels (7, 8).

The “bio ink” consists of fluids with stem cells injected into the scallop. There are different combinations of fluids and cells used, but none has been approved by the FDA yet.

The third phase is to put together the scallop and bioink in a piece of tissue to be implanted into the damaged myocardium (7-9). Techniques based on direct injection of bioink, extrusion or laser use are described. The final result is good enough to permit development of new clinical studies (7-9).

Myocardial regeneration by mechanical support

In the last years, the mechanical support of the heart has been increasingly developed because the number of heart transplant is limited by the small number of donors. The artificial heart was used for the first time by Kolff *et al* in 1957 (10), but since then, and especially in the last 20 years, the technique has developed dramatically. At present, the new generation of ventricular assist devices (VAD) are implanted into the myocardium, with minimal friction inside the pump, which is kept in the position by magnetic levitation, and the very new generations will have their batteries charged in a Wi-Fi manner, in rooms with magnetic resonators (11, 12).

Ventricular assist devices, and especially left ventricular assist devices (LVAD), are now used not only as “bridge to transplant” but also as “destination therapy”, which is a special indication in the ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure (13). This is due to the extraordinary observation that, in some patients with advanced heart failure and dilated cardiomyopathy, in whom the cause of the heart failure cannot be removed, the myocardial function recovers after several months of mechanical support in such a degree that sometimes the LVAD can be explanted (11, 12). Studies show that this is a possible explanation in about one third of patients with dilated cardiomyopathy, mainly idiopathic. The exact mechanism of this recovery is not completely understood. Some authors believe that at macroscopic level, the ventricle regains its contractility, but at molecular level, the new myocardium is different from the healthy myocardium before the development of heart failure (14). That is why the phenomenon of regaining contractility of the failing myocardium by simple prolonged mechanical support is considered an important field of research, in order to develop a new therapy in advanced heart failure.

Other methods

From some other methods developed in the field of myocardial regeneration, one important category is emerging: the use of gene engineering. A good example is the injection of micro messenger RNA in the damaged myocardium, which

leads to proliferation of myocytes – phenomenon which changes all the above-discussed concept that the adult myocardium does not proliferate. Two examples of experimental studies (15, 16) may suggest that our old theories of the heart as a non-mitotic organ will be completely changed in the near future by gene interventions. □

REFERENCES

- MacLellan WR, Schneider MD.** Genetic dissection of cardiac growth control pathways. *Annu Rev Physiol* 2000;62:289-319. doi: 10.1146/annurev.physiol.62.1.289.
- Anversa P, Leri A, Kajstura L.** Cardiac Rgeneration. *JACC* 2006;47:1769-76. doi: 10.1016/j.jacc.2006.02.003.
- Leong YY, Ng WH, Ellison-Hughes GM, Tan JJ.** Cardiac Stem Cells for Myocardial Regeneration: They Are Not Alone. *Front Cardiovasc Med* 2017;4:1-13. doi: 10.3389/fcvm.2017.00047.
- Cinteza M.** Gene Therapy and Cardiomyocyte Transplant in Heart Failure. *Maedica J Clin Med* 2014;3:229-231. PMID: PMC4305989.
- Lemcke H, Voronina N, Steinhoff G, David R.** Recent Progress in Stem Cell Modification for Cardiac Regeneration. *Stem Cells Int* 2018;2018:1-22. <https://doi.org/10.1155/2018/1909346>.
- Gherghiceanu M, Popescu LM.** Cardiac telocytes – their junctions and functional implications. *Cell Tissue Res* 2012;348:265-279. doi: 10.1007/s00441-012-1333-8.
- Richards D, Iia J, Yost M, et al.** 3D bioprinting for vascularized tissue fabrication. *Ann Biomed Eng* 2017;45:132-147. doi:10.1007/s10439-016-1653-z
- Pulcu N, Lee S, Doppler S, et al.** Bioprinting Approaches to Engineering Vascularized 3D Cardiac Tissues. *Curr Cardiol Rep* 2019;21:90. <https://doi.org/10.1007/s11886-019-1179-8>.
- Tomov ML, Gill CJ, Cetnar A, et al.** Engineering Functional Cardiac Tissues for Regenerative Medicine Applications. *Curr Cardiol Rep* 2019;9:105. doi: 10.1007/s11886-019-1178-9.
- Cook JA, Shah KB, Quader MA, et al.** The total artificial heart. *J Thorac Dis* 2015;12:2172-2180. doi: 10.3978/j.issn.2072-1439.2015.10.70.
- Garbade J, Bittner HB, Barten M, Mohr FW.** Current Trends in Implantable Left Ventricular Assist Devices. *Cardiol Res Pract* 2011;1-9. doi:10.4061/2011/290561
- Zimpfer D, Fiane AE, Larbalestrier R, et al.** Long-Term Survival of Patients With Advanced Heart Failure Receiving an Left Ventricular Assist Device Intended as a Bridge to Transplantation: The Registry to Evaluate the HeartWare Left Ventricular Assist System. *Circ Heart Fail* 2020;13:e006252. DOI: 10.1161/CIRCHEARTFAILURE.119.006252.
- Ponikowski P, Voors AA, Anker SA, et al.** 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). *European Heart Journal* 2016;37:2129-2200. <https://doi.org/10.1093/eurheartj/ehw128>.
- Castillero E, Ali ZA, Akashi H.** Structural and functional cardiac profile after prolonged duration of mechanical unloading: potential implications for myocardial recovery. *Am J Physiol Heart Circ Physiol* 2018;315:H1463-H1476. doi: 10.1152/ajpheart.00187.2018.
- Eulalio A, Mano M, Dal ferro M, et al.** Functional Screening Identifies miRNAs Inducing Cardiac Regeneration. *Nature* 2012;7429:376-381. doi: 10.1038/nature11739.
- Lesizza P, Prosdocimo G, Martinelli V, et al.** Single-Dose Intracardiac Injection of Pro-Regenerative MicroRNAs Improves Cardiac Function After Myocardial Infarction. *Circ Res* 2017;8:1298-1304. doi: 10.1161/CIRCRESAHA.116.309589.