



EVAGELISMOS GENERAL HOSPITAL OF ATHENS
A' DEPARTMENT OF CARDIOLOGY

July 2012 • Volume 7 • No 3 (27)

ISSN: 1792-7919

e-ISSN: 1792-7927

RHYTHMOS

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EDITORIAL

Biological Pacemaker: Science Fiction or a Feasible Project?

Antonis S. Manolis, MD

First Department of Cardiology, Evangelismos General
Hospital of Athens, Athens, Greece

Artificial electronic pacemakers have been successfully driving the hearts and reliably saving the lives of millions by providing cardiac pacing for a variety of cardiac bradyarrhythmias. However, there are several caveats to this technology not merely limited to procedural and hardware complications associated with its usage. These hurdles have prompted research in the development of a biological counterpart which could replace or supplement its electronic version. The concept of the biological pacemaker is very appealing, albeit most challenging. If normal working myocytes or conduction system cells could be transformed to perform the pacemaker function, there would be no need to replace pulse generator, and no issues with circuit or lead failure, size mismatch or foreign body infection would ever arise. Two general approaches have been pursued in the development of biological pacemakers, *gene transfer* into cardiac myocytes to create or enhance the pacemaker function, and *cell transplantation* into the heart that can perform the pacemaker function on their own or in conjunction with native cardiac myocytes.^{1,2} There are always pros and cons of these different approaches. Importantly, in order to develop such a biologic

pacemaker, two elements are deemed essential: to select a gene that can direct cells of non-automatic tissue to induce spontaneous phase 4 depolarization in a reliable and automatic manner, similar to the native sinus node cells or other conduction tissue with inherent automaticity; and subsequently to develop a technique to deliver this gene into the target tissue. Gene transfer methods may use injection of adenoviral vectors, of genetically engineered stem cells or use of gene-carrying mesenchymal stem cells.¹ Thus, biologic pacing could be accomplished either by genetic engineering, cellular therapy or a combination of both. Over the past decade, gene therapy has been explored to upregulate β_2 -adrenergic receptors, to downregulate inward rectifier current, and to overexpress pacemaker current as potential sources of biological pacemakers. Cell therapy approaches have explored the “forcing” of embryonic stem cells to evolve along cardiac pacemaker cell lines and the use of adult mesenchymal stem cells as platforms for delivery of specific gene therapies.²

Cardiac ion channels and calcium handling proteins forming the key molecular components of the native cardiac pacemaker action potential were the primary candidates for gene therapy based biological pacemaking. Modulation of ion channels and other pacemaking associated proteins, either by gene delivery/ cell therapy or a combination of both are being intensely and thoroughly investigated. Pluripotent/ multipotent stem cells serve as excellent vehicles for carrying such genes, which have been modified to ensure that the implanted

cell transforms into a pacemaker-like cell. Implantation of hybrid/ tandem pacemakers could protect against the risk associated with the malfunction of either the biological or artificial pacemaker in the patient. Some of these gene- and cell-based approaches aim at manipulating the basic determinants of native pacemaker function in normal hearts. Techniques employed to attain these targets include gene transfer via viral infection or naked plasmid transfection, use of embryonic stem cells that incorporate a complement of native genes, or adult mesenchymal stem cells engineered as platforms to carry pacemaker genes. More recently methods have emerged to reproduce pacemaker action potentials in noncardiac cells and/or to induce fusion of noncardiac and cardiac cells. The aim remains to identify gene(s) which optimize heart rhythm avoiding excessive bradycardia or long pauses, but also provide a physiological rate response based on metabolic and/or catecholamine status.

Initial attention of biologic pacing has been focused on one particular target, the hyperpolarization activated, cyclic nucleotide gated (HCN) gene isoforms responsible for the funny (If) pacemaker current, which is highly expressed in the natural pacemaker, the sinoatrial node, as well as in the atrio-ventricular (AV) node and the Purkinje fibers of conduction tissue.³ The If current controls the rate of spontaneous activity of sinoatrial myocytes, hence the heart rate. The reason for which investigators of biologic pacing persist in this direction relies on the evidence that the If current alone appears to be adequate, whether administered via virus or via platform, to drive the heart. Initial data indicate that both gene and cell therapy approaches can result in effective biological pacemaker function over a period of weeks in intact animals. Indeed, the use of adult human mesenchymal stem cells as a platform for carrying pacemaker genes has resulted in the formation of functional gap junctions with cardiac myocytes in situ leading to propagation of pacemaker current. These approaches are encouraging, suggesting that biological pacemakers based on this strategy can be brought to clinical testing.^{3,4} The invention of Dr. Rosen and colleagues comprises a “nanofilm-encapsulated biological pacemaker, composed of a collection of adult human mesenchymal stem cells that are modified to mimic the natural human pacemaker's ability to generate and conduct electrical current, thereby recreating natural pacemaker function of the heart”.⁵ When implanted in the myocardium, this platform could potentially stimulate impulse initiation and propagation hopefully without any adverse effects. With use of adult human mesenchymal stem cells as delivery systems, the investigators were able to provide a means for administering catecholamine-

responsive biological pacemakers into the left ventricular myocardium of adult dogs (afflicted by complete heart block and having backup electronic pacemakers) that functioned in a stable manner for 6 weeks and manifested no cellular or humoral rejection.⁶

There is still a long way to go until we have more practical and simplified approaches to this novel therapy. Only recently, did investigators report the use of venous catheters to create a biological pacemaker, using off-the-shelf clinical equipment in a large animal model (pigs), paving the way to direct translational medicine to materialize itself.⁷ They injected an adenoviral vector cocktail, expressing dominant-negative inward rectifier potassium channel (Kir2.1AAA) and hyperpolarization-activated cation channel (HCN2) genes, into the AV junctional region via a catheter advanced through the femoral vein. However, this experiment provided only temporary (2 weeks) support and may only be considered for cases of pacemaker infection requiring explantation as a bridge-to- device pacing for the effective clearance of infection prior to the reimplantation of a new electronic pacemaker, thus avoiding the indwelling electrocatheter needed for temporary pacing.

However, a potential concern about biological pacemakers is the possibility that they might malfunction to trigger, depending on the implant site, atrial or ventricular tachyarrhythmias. Although no arrhythmic activity was reported with use of the HCN family of pacemaker channel genes to create biological pacemakers when viral vectors or adult human mesenchymal stem cells were employed as delivery platforms, nevertheless, in preliminary experiments, investigators discovered that canine left bundle branch implantation of an adenoviral construct of HCN induced ventricular ectopy or tachycardia.^{8,9} However, these If-associated arrhythmias could be controlled with If inhibiting drugs such as ivabradine, which appeared to suppress ventricular tachycardia more readily than sinus rhythm, which might confer a therapeutic benefit in such circumstances.⁹

Until a tangible and more realistic result has been effected, there is a need, at least during clinical trials, to implant an electronic alongside with a biological pacemaker (tandem pacemaker approach). Of course for such an approach to succeed, one has to ensure that the dual system is synergistic and remains safe without adverse or unpredictable interactions between the biological and electronic pacemakers and confers more benefit to the patient than would an electronic pacemaker alone. There is indeed some preliminary evidence that biological pacemakers, like their electronic counterparts, can be regulated for basal heart rate and catecholamine responsiveness (rate response),¹⁰ or might be able to

respond to physiological emotional arousal, and increase their pacemaker function.¹¹ The concept is to have the electronic pacemaker provide a bridge to biological pacing therapeutics, until there is more solid evidence for the safety and efficacy of this revolutionary novel approach.

Whether the end result of the application of all these preliminary data will be a clinically applicable biological pacemaker remains to be proven. Although proof of concept has been demonstrated, there is still a long way to go and many obstacles to overcome before its safe and reliable clinical application. First, one needs to identify the ideal candidate pacemaker cells, and second to make headway in fine-tuning the behavior of these pacemaking cells, while finally monitoring and controlling the interactions between the pacemaker and host myocardium. Thus, there is still need for development of new technologies and more testing in the animal laboratory to enhance our understanding of mechanisms that control gene expression and cell coupling until the biological pacemaker becomes a feasible and realistic project. Meanwhile, electronic pacemaker systems have proven their value, while they are still rapidly evolving and for now remain the main and only player in the field.

As the inventor himself, Dr Michael Rosen,¹² has put it, in order to “see biological pacemaking in our lifetime”, the following are needed: “For virus or stem cell, we need evidence that it is superior to the electronic pacemaker in terms of adaptability to the body’s physiology and duration of effectiveness; evidence regarding long-term incidence of inflammation, infection, rejection, neoplasia; evidence for/against long-term proarrhythmic potential; localization at site of implantation vs migration to other sites; other toxicity; optimization of delivery systems”. “For stem cell (embryonic, mesenchymal), we need evidence regarding persistence of the administered cell type vs differentiation into other cell types; in the latter event, evidence regarding persistence of pacemaker function (current and coupling)”.

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Long-Term Results of Atrial Fibrillation Ablation

Sokratis Pastromas, MD

Department of Cardiology, Evagelimos Hospital, Athens, Greece

Although the initial ablation procedure has a modest acute success rate (~70%) in patients with atrial fibrillation (AF), a repeat procedure adds significant improvement (~80%). The short- and mid-term results may offer some encouragement, however the longer-term results are sobering with arrhythmia-free survival rates diving to around 30%. Nevertheless, this disappointing rate may increase significantly with a second procedure to around 60%. Such data of the long-term results of AF ablation are herein reviewed.