Editorial

# Cardiac Pacemakers for the New Millennium

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A recent correspondence to the *New England Journal of Medicine*[1] was highlighted in the *New York Times* under the heading "In a High-Tech World, Pacemaker Risks Rise".[2] The focus of the *New England Journal* article was a Swiss patient with an AV-sequential pacemaker who was using an alternative medicine device called a Zapper. This device is held in both hands and generates electrical impulses. In the patient's case, use of the Zapper was associated with recurrent episodes of fainting over several months. At each faint he evidently dropped the Zapper and proceeded to recover. Subsequent workup revealed that high frequency signals at a rate of about 140 bpm were induced by the Zapper causing brief periods of ventricular oversensing with inhibition of the pacemaker. *The Times* quotes Dr. Sergio Pinski in implicating other modern conveniences that have been associated at times with improper pacemaker function: these include percutaneous electrical nerve stimulation for treatment of pain, use of cell phones, passing through metal detectors, and use of magnetic resonance imaging. While the number of patients put at risk by some of these environmental exposures is not large, information such as this is a cause of unease to patient, physician, and manufacturer.

This is not the limit of concerns regarding pacemaker therapy, however. Among their other shortcomings are their inability to respond optimally to physiologic demands for varying heart rate during work, exercise or changing emotional state; the limitations imposed on unit and electrode dimensions by increasing age and mass of the pediatric patient; the inability to individualize for each patient optimal activation and contraction patterns because the need for electrode stability limits access to some sites in the heart; and the life expectancy of the pacemaker battery, which must be tested and replaced periodically.

Concerns such as those reviewed above have encouraged advances in electronic device development and manufacture (see, for example, Zivin and Bardy[3]) as well as the search for alternatives to electronic pacemakers. The major breakthrough here has been recent research in biological pacemakers. This breakthrough includes a family of investigative efforts designed, literally, to "build" a new sinoatrial node. The approaches used have been those of gene therapy, wherein the normal gene component of cardiac cells is modified to alter cardiac rate and rhythm; and/or cell therapy wherein embryonic stem cells or adult mesenchymal stem cells have been explored as biologically-based (rather than electronic) pacemaker units.

Three strategies have been reported to create biological pacemaker activity: upregulation of the effects of the sympathetic nervous system on impulse initiation;[4,5] reduction of outward, repolarizing

current that tends to prevent the cells of the heart from initiating spontaneous impulses;[6] increasing inward current during diastole.[7] The first strategy[4,5] is one in which the gene encoding the $\beta_2$-adrenergic receptor was incorporated in a plasmid and injected via catheter into the atria of pigs. It was reasoned that if the gene achieved uptake into a reasonable subset of atrial cells, these would manifest increased responsiveness to the effects of endogenous or administered $\beta$-adrenergic agonist resulting in an increase in atrial rate. In other words there was no attempt to increase the number of cells with pacemaker current per se: rather, the goal was to increase the responsiveness of endogenous pacemaker mechanisms to $\beta$-adrenergic stimulation. This end point was in fact realized with an increase in the atrial rates of pigs on day 2 after plasmid administration. The effect, however, was short-lived, disappearing 24 hours later.

The next two gene therapy strategies reported were based on knowledge of the ion currents that operate during phase 3 repolarization and phase 4 depolarization of the cardiac action potential. In brief, inward currents operating during these intervals depolarize the membrane while outward currents hyperpolarize the membrane. Both strategies used an adenoviral construct to deliver the gene of interest. Miake et al proposed a plan to downregulate the outward, hyperpolarizing potassium current, $I_{K1}$.[6,8] They did this by replacing three amino acid residues in the gene encoding one of the pore-forming subunits of the potassium channel, Kir2.1. Using an adenoviral vector injected into the left ventricular cavity of guinea pigs, they achieved 80% suppression of $I_{K1}$ after 3-4 days. Spontaneous rhythms were demonstrable on ECG and phase 4 depolarization and pacemaker activity was evident in action potentials recorded from ventricular myocytes isolated from these hearts.

In another approach, our laboratories overexpressed the inward depolarizing current, $I_f$, which is the primary pacemaker current of the heart.[9,10] The channel encoding $I_f$ is the HCN (hyperpolarization activated, cyclic nucleotide gated) family of gene products.[11,12] When the HCN2 isoform was packaged in an adenoviral construct If overexpression was achieved in rat ventricular myocytes in culture,[13] and at sites at which the construct was injected into the atria[7] and the ventricular conducting system (left bundle branch[14]) of dogs. In cell culture a significantly greater beating rate was seen with HCN2 than in controls,[13] and responsiveness of both to the positive chronotropic effects of isoproterenol and to the negative chronotropic effects of acetylcholine was demonstrable.[15] In the intact animals escape rhythms were achieved, apparently originating at the sites of atrial[7] and left bundle branch[14] injection. This evidence was obtained at days 3-7 after injection.

Of the three gene therapy approaches, only $I_f$ overexpression has manifested stable escape rhythms having physiologically-acceptable rates and autonomic responsiveness. Although $\beta_2$-adrenergic receptor overexpression was an autonomically based approach, the effect was very transient and was targeted at pacemaker modulation rather than pacemaker creation. The strategy of $I_{K1}$ suppression to reduce outward current raises the concern of prolongation of repolarization and the potentially problematic accompaniment of proarrhythmia. Finally the gene therapy approaches that are dependent on viral vectors are problematic in that using replication-deficient adenoviruses, genetic material is not incorporated into the genome and any effect is transient. Other viral vectors introduce infectivity and neoplasia.

An alternative to gene therapy is provided by cell therapy. In very preliminary studies related to the development of biological pacemakers, subpopulations of embryonic stem cells have been found to initiate impulses similarly to pacemaker cells,[16] although whether this impulse initiation is based on the $I_f$ current or has another ionic basis is not known. These cells are currently being explored as potential biological pacemakers. Current concerns are that immature embryonic stem cells can terminally differentiate and lose their pacemaker characteristics. Hence, driving these cells down a cardiac lineage to achieve a uniformly stable sinus node is an important challenge to be overcome. Also to be determined is the arrhythmogenic potential of these cells,[17] as well as immunogenicity and potential for neoplasia.

Our laboratories have studied the use of adult human mesenchymal stem cells as a platform to deliver the pacemaker gene HCN2 to the heart. These cells putatively have little immunogenic potential,[18] although this observation awaits rigorous testing. Very importantly, they form electrophysiologically functional gap junctions with cardiac myocytes both in isolated cell systems[19] and in the heart in situ.[20] The resultant cell coupling ensures that information in the form of ion currents incorporated in the stem cells can be transmitted to the myocytes. We have used electroporation (thereby avoiding viral vectors) to load these stem cells with the HCN2 gene, leading

to overexpression of pacemaker current, and have shown that coculture of these stem cells with cardiac myocytes or injection of about one million of these stem cells as a node into the ventricle generates stable pacemaker activity.[20] In the intact heart this is seen 4-7 days after injection as a stable idioventricular rate of about 60 bpm on induction of transient heart block.[20]

Concerns about stem cell therapies in addition to those mentioned above include differentiation into other cell lines, migration to other sites in the body, immunogenicity, potential for malignancy, as well as duration and stability of effect.

In conclusion, in less than a decade tremendous advances have been made in gene and cell therapies that promise to take the pacemaker field from its already sophisticated level of excellence to a completely new plateau of possibilities. While a number of questions remain to be answered, the possibility of supplementing and eventually replacing a superb example of electrical and computer engineering, the electronic pacemaker, with a pacemaker that is engineered biologically has clearly reached the level of warranting serious consideration. In making this statement, we should temper it with the reminder that none of the gene or cell therapy approaches discussed have yet been tested in direct comparison to electronic pacemakers with regard to efficacy and duration of effect. And this must be done if these new approaches are to achieve long-term clinical application.

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