A Paradigm Shift in Cardiac Pacing Therapy?

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Artificial pacemakers have been continuously improved since 1949, when Jack Hopps, from the National Research Council of Canada in Ottawa, first assembled an external generator for Wilfred Bigelow and John Callaghan in the basement of the Banting Institute at the University of Toronto. Although Hopps’ device was not the first artificial pacemaker, the presentation by Callaghan at the 1950 American College of Surgeons meeting in Boston, Mass, stimulated a surge of experimentation that quickly led to demonstration of the utility of cardiac pacing in humans and subsequent manufacture of implantable devices. Since that time, remarkable advances in lead design, battery duration, programming capability, and electronic circuitry have given rise to one of the most successful and accepted life-saving, palliative therapies in modern medicine. Furthermore, medical indications for pacing therapy have expanded beyond the management of symptomatic bradycardia to include treatments for hypertrophic cardiomyopathy, neurocardiogenic syncope, ventricular tachyarrhythmia, congestive heart failure, and atrial fibrillation. Nevertheless, in spite of the fact that pacemakers represent a state-of-the-art technology, there are significant problems associated with long-term cardiac pacing.

The permanent implantation of an electronic pacemaker device is associated with complications that “... vary in clinical significance from benign to life-threatening.” These include the need for replacement of generators (primarily attributable to limited battery life) and leads (because of fracture, displacement, inappropriate stimulation, loss of insulating material, or tissue perforation). These problems are often exacerbated in pediatric patients owing to their size and the demands imposed by growth. Other complications include infection, thrombosis, valve dysfunction, maladaptive cardiac remodeling, and a lack of autonomic neurohumoral responsiveness. Thus, pacing therapy, although effective, continues to have important limitations. Although further refinements in the longevity and size of devices, lead biomaterials, and microprocessors seem inevitable, on the basis of the above concerns and escalating treatment costs, a handful of investigators have begun to consider other approaches to cardiac rhythm management.

In recent years, there have been a number of studies published that describe efforts to replace or complement artificial pacemaker devices with a biology-based method to treat sick sinus syndrome or atrioventricular (AV) conduction block. Most of these employed 1 of 3 principal means to either stimulate function of the native pacemaker or create ectopic pacemaker foci, namely: (1) gene transfer to existing cardiomyocytes, (2) cellular transplantation, or (3) delivery of genetically modified cells to the heart. The first of these experiments demonstrated that injection of plasmids encoding the β2-adrenergic receptor increased heart rate in mice or pigs. Subsequently, fetal10,11 and neonatal12 cardiac cells or spontaneously contracting, embryonic stem cell–derived cardiomyocytes13,14 were shown to functionally integrate and act as an ectopic pacemaker when transplanted into the left ventricular free wall of dogs, pigs, or guinea pigs. Similarly, cardiomyocytes infected with adenoviral constructs to inhibit Kir2-encoded inward-rectifier potassium channels in the ventricle15 or overexpress the hyperpolarization-activated, cyclic nucleotide–gated (HCN) channel HCN2 in either the atrium or ventricle16,17 were sufficient to produce spontaneous pacemaker activity. The latter result was essentially reproduced by transplanting human mesenchymal stem cells transfected with murine HCN2 into the left bundle branch of dogs with transient AV block. In contrast, our laboratory recently described implantation of engineered tissue containing skeletal myoblasts to create a permanent AV electrical conduit for eventual treatment of complete heart block rather than increasing heart rate or creating ectopic sites of pacing. Despite methodological differences, all of these studies have contributed important experimental proofs-of-principle, each with inherent strengths and weaknesses, which is a situation reminiscent of the variability in early electronic pacemaker designs.

In this issue of Circulation, there are 2 reports that describe how alterations in HCN channel genes enhance the ability of transduced cardiomyocytes to function as autonomically responsive ectopic pacemakers. Accumulating evidence suggests that HCN proteins represent rational candidates for gene transfer approaches to create a “biological pacemaker.” This is because the ionic basis for spontaneous, diastolic depolarization (and hence pacemaker activity) is the generation of a hyperpolarization-activated inward cation current, I_h. HCN proteins are largely responsible for generating the “funny” current (I_f), which results from permeability of these channels to both Na+ and K+. In addition to their unusual voltage dependence, Autonomic stimulation modulates the voltage dependence of HCN channel activation without changing the total current, thereby altering the slope of diastolic depolarization and heart rate. For example,
β-adrenergic agonists cause cAMP-mediated increases in \( I_f \), most likely due to allosteric modification of HCN channels, with cAMP binding preferentially to open channels and locking them in that state. This shifts the activation curve in a more positive direction, which in turn generates more inward current at diastolic membrane potentials, increasing the rate (slope) of diastolic depolarization and consequently heart rate. The effect of muscarinic agonists (eg, acetylcholine) are opposite, leading to decreases in \( I_f \) by shifting the activation curve toward more negative voltages, resulting in less inward diastolic current, decreasing the slope during this phase of the activation sequence, and thus, slowing heart rate.23

Tse et al21 chose to modify murine HCN1 by deleting 3 amino acids from the S3-S4 linker region to favor channel opening. The recombinant gene, called HCN1-ΔΔΔ, was then cloned into a bicistronic shuttle vector, which allowed for the simultaneous expression of green fluorescent protein, and the construct was packaged into adenoviral particles.21 In contrast, Bucchi et al20 introduced a point mutation in the murine HCN2 gene to induce a positive shift in the channel activation threshold. The recombinant gene was termed mE324A, and it was subsequently cloned, packaged, and amplified with standard procedures.20 Consequently, each laboratory studied these recombinant channels in both cell cultures and whole animals to determine their biophysical properties and physiological responses.

Using a number of technically demanding experimental procedures, Tse et al21 elegantly demonstrated that adult cardiomyocyte cultures (ie, atrial and ventricular) and guinea pigs hearts exhibit automaticity with a normal firing rate and spontaneous generation of action potentials from the site of the HCN1-ΔΔΔ adenovirus injection, respectively.21 The authors go on to show, in a porcine model of experimental sick sinus syndrome, that the same adenoviral construct could transduce a relatively small number of atrial cardiomyocytes and still create a surrogate sinoatrial node that generated a physiological heart rate for up to 14 days. In addition, their “biological pacemaker” was sensitive to catecholamines, even though HCN1 is the least cAMP-responsive of the studied HCN channel protein isoforms.21,23 Correspondingly, Bucchi et al20 found their mE324A channel protein was remarkably sensitive to catecholamines (compared with HCN2), and the expression of either of these proteins in the left bundle branch of dogs with complete AV block increased the basal heart rate.20 Interestingly, in culture experiments, current traces for cells transduced with the mE324A protein appeared to resemble the activation kinetics expected for HCN120; however, direct comparisons with the results from Tse et al21 are not possible because HCN channels tend to show more positive pacemaker current activation in neonatal cardiomyocytes.21 In any event, mE324A channels opened faster than mHCN2 channels, yet, curiously, fewer cells were infected with the adenovirus that contained the recombinant protein.

Therefore, both research groups have extended previous findings that used gene transfer of wild-type pacemaker channel genes to demonstrate that genetically engineered HCN channels offer distinct advantages in terms of their activation kinetics and neurohumoral responsiveness. In addition, these researchers have moved toward overcoming the problem of slower-than-normal heart rates seen in some earlier studies13–17 and have demonstrated that biological pacemakers reduced the dependence on electronic pacemaker devices, which suggests that a combination of the 2 therapies would provide a fail-safe mechanism.20,21

The exciting, clinically relevant findings described in these articles suggest that human trials may be on the horizon; however, such trials would be premature. Because artificial pacemakers already provide a reliable, proven means for palliation of sick sinus syndrome and complete heart block, there is no immediate scientific or ethical justification to rush this technology into humans. There are simply too many shortcomings in each of the technologies developed thus far to attempt a biological pacemaker treatment for severe bradycardia, even if combined with an electronic device. With respect to the presently discussed research, the most obvious of these, as pointed out by both Tse et al21 and Bucchi et al,20 is the transient nature of gene expression by episomal adenoviral vectors. Function over a period of days, weeks, or even months in a human heart would, at best, replicate the findings in large animals and, at worst, result in a catastrophic failure because of arrhythmia or other unanticipated consequences.

Much remains to be learned at the preclinical level about the effects of heteromultimerization between recombinant and endogenous \( I_f \) channel proteins, as well as injection-site trauma, accuracy of vector delivery, immunological responses, and precise control of gene expression, all of which warrant continued experimentation in animals. Furthermore, long-term studies with adeno-associated viruses or retroviruses (including lentiviruses) to achieve chromosomal integration of a transgene may be held back by safety concerns. The same can be said for cell transplantation methods, whether the cells are genetically modified or not. In these instances, the possibility of tumor formation, electrical remodeling of the cells, inflammation and rejection, fusion with recipient cardiomyocytes, proper electromechanical integration, long-term cell survival and function, and the potential for arrhythmogenesis continue to be the salient issues. In some respects, the current state of the biological pacemaker is similar to where the electronic pacemaker was in the 1960s and early 1970s. In describing the first modern pacemaker, Lidwell stated that “... its use does not require very much intelligence.”2 The treatment of humans with biological pacemakers will clearly require not only intellect but comprehensive preclinical testing to determine whether such devices can come close to the reliability, longevity, and utility of their electronic relatives.

Acknowledgments

Drs Cowan and McGowan are supported by grants from the National Institutes of Health (HL-068915, HL-066186, and HL-074374) and the Cardiac Conduction Fund at Children’s Hospital Boston.

Disclosures

None.
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Circulation. 2006;114:986-988
doi: 10.1161/CIRCULATIONAHA.106.644799
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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