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Can Biological Pacemakers Respond to Physiological Emotional Arousal?

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When the function of the sinoatrial node or the atrioventricular conduction system of the heart is impaired by disease processes, atrial and/or ventricular pacing by an artificial electronic pacemaker maintains the heartbeat. The functionality and capability of electronic pacemakers have been improved steadily over the last 5 decades. Currently, an electronic pacemaker is one of the most successful, life-saving palliative therapies in modern medicine.

However, electronic pacemakers are not without problems and limitations. Their batteries need replacement. The electrodes can fail. Electronic pacemakers in pediatric patients have a size mismatch issue with the growth of the patients. Complications such as infection and thrombosis can occur. Finally, there is a nuisance, if not a life-threatening situation, with electronic pacemakers. In order to meet the demands of physical and emotional activities of daily life, the beating rate of a normal heart is under constant autonomic neurohumoral regulation. For example, when exercising the heart rate can go from ~ 60 beats per minute (bpm) to more than 150 bpm in a matter of minutes. An electronic pacemaker cannot respond to the autonomic neurohumoral regulation.

The concept of the 'biological pacemaker' is an appealing one. If normal working myocytes or conduction system fibers can be made to perform the pacemaker function, then there is no need to change the battery, no issue with electrode failure or size mismatch. There have been two broad approaches in the development of biological pacemakers: by transferring genes into cardiac myocytes to help or create the pacemaker function, and by transplanting cells into the heart that can perform the pacemaker function on their own or in conjunction with native cardiac myocytes. The pros and cons of these different approaches have been discussed in great details in excellent recent reviews^{1–3}.

Currently, the approaches of creating biological pacemakers have coalesced to the transfer of genes encoding the hyperpolarization-activated, cyclic nucleotide-regulated (HCN) cation channels, or the delivery of cells overexpressing HCN channels. This makes perfect sense because the HCN channels underlie the normal pacemaker function of the heart. Their cAMP binding domain enable them to respond to autonomic regulation: β -adrenergic stimulation leads to a rise in cAMP and an increase the pacemaking rate, while muscarinic stimulation leads to a drop in cAMP and a decrease the pacemaking rate. Biological pacemakers created by transferring HCN genes or cells loaded with HCN channels have the

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potential to be responsive to autonomic stimuli. Such ‘smart’ pacemakers will be able to better meet the physical and emotional demands of the body, and improve the quality of life.

Previously, two groups have shown that catecholamine infusion can increase the beating rates of biological pacemakers created by transfer of HCN genes into the heart ^{4, 5}. Thus, the concept has been proven effective by experimental interventions. But can biological pacemakers respond to physiological stimuli, such as emotional arousal or physical activity? In the study by Shlapakova *et al* of this issue of Heart Rhythm ⁶, investigators of the Rosen group teamed up with Verrier to take on this issue. The experiments required demanding procedures as in the previous publications from the Rosen group. A pacemaker lead was introduced into the right ventricular apex. Complete AV block was created by radiofrequency ablation of the AV node. Adenovirus carrying the murine HCN2 gene (Ad-HCN2), mixed with adenovirus carrying enhanced GFP (AdGFP) as a reporter, was injected into 3 sites identified by left bundle branch (LBB) electrograms through a catheter. After each injection, cardiac pacing via the injection catheter was performed for pace mapping (as a reference for future tests of the origin of pacemaker activity). Control dogs went through the pacemaker implantation and AV block procedures, but with saline injections. On day 1 and day 7, Ad-HCN2 dogs and control dogs were tested for their response to emotional arousal, created by food presentation after overnight fasting. The response was evaluated by 30 min ECG monitoring. The data were analyzed by Poincare plots, which produced the following parameters: average RR interval, instantaneous beat-to-beat variability of the RR intervals, and continuous, longer-term versus instantaneous variability of the RR intervals.

On day 1, when the injected Ad-HCN2 had not been expressed yet, ad-HCN2 dogs and control dogs showed similar and minimal response to emotional arousal. By day 7, the HCN2 gene in virus-injected dogs was expected to have been fully expressed. Ad-HCN2 dogs showed a more prominent response to emotional arousal. Relative to the control dogs, the heart rates of ad-HCN2 dogs increased more and displayed more dynamic heart rate variations during the 30 min monitoring after food presentation. These data are interpreted as indicating that the biological pacemaker created by expressing murine HCN2 gene in the left bundle branch was able to respond to physiological emotional arousal, and increased their pacemaker function.

While the results are encouraging, there are a few issues in the current study that need to be more fully addressed in future experiments. First, in ad-HCN2 dogs examined on day 7, the increase in heart rate upon the very strong emotional arousal is modest. In the representative case shown, the heart rate increased from 45 to 72 bpm. Given the high titer of adenoviruses delivered to each dog (3×10^{10} fluorescent forming units each of ad-HCN2 and adGFP), is this the ceiling of autonomic responsiveness of HCN2-based biological pacemaker in the dog model? Second, the degree and location of exogenous HCN2 gene expression was not tested, and there was no pace mapping to confirm the LBB origin of the pacemaker function in the ad-HCN2 dogs.

These two issues are related. Can the autonomic responsiveness of a biological pacemaker be enhanced to eventually reach a heart rate of 150 bpm when in vigorous physical activity? Can this be done by increasing the dosage of gene transferred? Given the high virus titer, the injection volume and the number of injection sites, has the dosage of HCN2 gene transfer reached the limit in the current study? If so, can one improve the biological pacemaker performance by increasing the durability of gene expression, for example, by repetitive administrations of HCN gene carried by lentivirus, which by genome integration can reach long-lasting and accumulative effects?

Biological pacemakers have been created using gene therapy or cell implantation. The clinical needs for gene therapy and cell implantation are not limited to creating biological pacemakers. In principle, gene therapy may be useful in treating congenital disorders, such as arrhythmia-inducing channelopathies. Cell implantation holds the promise of repairing myocardium damaged by infarction or other injuries. Both therapeutic modalities have major technical obstacles and safety concerns. The promise of biological pacemakers can be realized only when the major technical obstacles and safety concerns facing gene and cell therapies are resolved. Before that time, the contributions made by Rosen and colleagues are commended – they bring the hope to patients suffering pacemaker malfunction that a ‘cure’ is possible one day ¹.

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