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EDITORIAL

Leadless Pacing: The Future is not Here Yet!

Antonis S. Manolis, MD

First Department of Cardiology, Evagelismos Hospital,
Athens, Greece

Despite great technical advances over the last decades, cardiac pacing is still associated with a significant rate of complications mostly ascribed to the pacing leads.¹ Leads are susceptible to mechanical stress, whether transvenous or epicardial, and constitute the pacing component most prone to failure; they are the major contributor to complications, may cause vascular obstruction, and other late complications, such as mechanical failure and infection, whereby extraction is required with its attendant dire consequences. Implantation of a pacemaker in young patients exposes them to high risk of subsequent lead complications, and when failed leads are replaced without extraction, the presence of multiple endocardial leads may cause major vascular morbidity. New devices for bi-ventricular or bifocal pacing to effect cardiac resynchronization therapy (CRT) incorporating 3 leads are associated with even more problems. Hence, there came about a resurgence of interest in the technology of leadless pacing.

The first totally self-contained leadless pacemaker system was proposed by Spickler back in 1970 using a device powered by mercury-zinc and nuclear power that was successfully tested in animals.² Almost 30 years later, Gotto et al.³ tested an automatic power-generating system (AGS) which converts kinetic into electric energy

for quartz watches as a power source for cardiac pacemakers. They could demonstrate that the circuit generated pulses of 0.5 ms width at 1 Hz (60 pulses/min). The voltage of the AGS was maintained at 1.6 V while it was being charged by the accelerations. The generator supplied pulses of 0.75 V, 1.47 mA via a 510-ohm load. With fully charged AGS, the generator was also used to pace a mongrel dog's heart at 140 beats/min for 60 min. During pacing, the AGS supplied 420 mJ to the circuit and the cardiac muscle. The AGS was placed on the right ventricular wall of the dog under anesthesia. Energy of 80 mJ is stored in a capacitor by the heart beating at ~ 200 beats/min for 30 min. Thus, the AGS generated 13 microJ per heart beat. This result suggested that the AGS could supply enough energy for use in a cardiac pacemaker.

Several years later, Echt et al.⁴ explored the feasibility and safety of a technology enabling cardiac pacing without leads in an acute porcine model. The system comprised an *ultrasound transmitter* delivering energy from the chest wall to a receiver-electrode in contact with the myocardium that then converted the ultrasound energy to electrical energy sufficient to pace. In feasibility studies, the receiver-electrodes were attached to the tip of a catheter to facilitate intracardiac positioning at pacing sites. In safety studies, ultrasound energy was transmitted to both chest walls, and histopathologic examinations were performed to evaluate bioeffects due to ultrasound energy transmission. In feasibility studies, direct and ultrasound-mediated electrical pacing was demonstrated at 30 sites in the right atrium, right ventricle

(RV), and left ventricle (LV), at direct electrical pacing outputs of 1.4 ± 0.6 V and ultrasound-mediated electrical pacing outputs of 1.8 ± 0.9 V. Using 2 receiver-electrode catheters, biventricular pacing could be demonstrated. Microscopic evaluation revealed no evidence of mechanical or thermal bioeffects.

Wieneke et al⁵ developed a temporary leadless pacemaker system based on induction technology and tested its feasibility and safety in a pig model. The device included a transmitter unit implanted subcutaneously at the level of the heart and an endocardial receiver unit implanted at the apex of the RV. The transmitter unit was used as a generator of *alternating magnetic field* converted into a voltage pulse by the receiver unit. During testing, an alternating magnetic field of about 0.5mT was generated by the transmitter unit at a distance of 3 cm. Voltage pulses with a pulse width of 0.4 ms and voltage amplitude of 0.6–1.0 V were generated. These pulses were finally able to reliably stimulate the heart. The same group later in a goat model demonstrated that for any given endocardial position of the receiver unit, up to a distance of 10 cm between the subcutaneous transmitter and the receiver unit, reliable pacing using induction could be obtained.⁶ Energy consumption was mainly determined by distance and pacing threshold. In anatomically important distances up to 6 cm, energy consumption remains within reasonable limits.

Lee et al⁷ reported their experience with leadless cardiac pacing in 10 patients with use of externally delivered ultrasound which provided energy that was transformed into an electrical stimulus by a specially fabricated transducer positioned at the myocardial surface. The authors illustrated the potential for *ultrasonic energy* transmission to be “directed” at a particular cardiac chamber, the LV, and to be transformed into electrical energy of sufficient magnitude to pace relatively sick hearts. Ultrasound-mediated pacing was successful in all patients. The acoustic window validated by computed tomography was predicted by transthoracic echocardiography. The study demonstrated, using a line-powered ultrasound generator, the feasibility of ultrasound-based pacing in patients with severe LV dysfunction (ejection fraction $29\% \pm 5\%$). The longer-term goal would be to facilitate targeting an “optimal” LV pacing site for application of CRT.

Defaria Yeh et al⁸ also tested temporary leadless cardiac pacing using ultrasound energy in patients with NYHA class III or IV heart failure symptoms & LV ejection fraction $\leq 35\%$. An implantable LV stimulation system transferred energy from a subcutaneous transmitter to an endocardial receiver through tissue free of interfering lung or rib (‘acoustic window’). They used

echocardiography to evaluate acoustic window locations and sizes to determine the implant site for a transmitter. Among 42 patients, at least one adequate acoustic window was identified in 41. Patients with ischemic cardiomyopathy compared with non-ischemic cardiomyopathy had smaller heart size but larger acoustic windows in the right lateral and standing positions.

According to Wang et al,⁹ LV endocardial leadless pacing (LVLEP) using energy transfer from an ultrasound transmitter to an endocardially implanted receiver to stimulate the heart may offer some potential advantages. These may include greater choice of LV lead positions, possibly more rapid LV activation, lower capture thresholds compared with those obtained via the coronary sinus, reduced risk of phrenic nerve stimulation, superior stability of an active fixation endocardial receiver electrode, perhaps even less arrhythmogenic pacing, and finally elimination of lead-related complications, compared with conventional CRT implantation.

A novel implantable cardiac pacing system based on this concept was recently developed for treatment of heart failure by EBR Systems¹⁰ & Cambridge Consultants¹¹ (Wireless Cardiac Stimulation-LV System, WiCS®-LV, EBR Systems, Inc., Sunnyvale, CA, USA) and a clinical trial using the WiCS®-LV system is ongoing in Europe. The trial, entitled Wireless Stimulation Endocardially for CRT (WiSE-CRT), is evaluating the safety and feasibility in 100 patients with heart failure who are candidates for CRT. In the WiSE-CRT study, the receiver electrode catheter is positioned in the LV via a femoral arterial sheath using the retrograde transaortic approach.¹² On May 3, 2011, EBR Systems announced the first human implants of the WiCS® Wireless Cardiac System.

Able to pace the heart through wireless transmission of energy, the WiCS system consists of a leadless electrode (receiver) acting as an energy harvester and a transmit transducer array, which is an ultrasonic pulse generator. Piezoelectric components are ideal for use in electromechanical transducers and were supplied by Morgan Technical Ceramics (MTC, Bedford, Ohio, USA) to manufacture the two key components to the system, the transmitter and the receiver, helping EBR Systems to maximize the energy efficiency of the WiCS device and prolong the life of the device out to 3 years.

LVLEP may also have some potential disadvantages, including variable energy transfer efficiency with different energy transfer modes (e.g. ultrasound vs alternating magnetic field vs radiofrequency-RF),^{5,7,9} complex technology with regards to ability of leadless pacing systems to detect intrinsic events and inhibit pacing output when necessary, and potentially worrisome external electromagnetic interference with the devices.

At present, EBR Systems is not the only company working on leadless pacemakers. The North Dakota State University (NDSU) Research Foundation, NanoStim with St. Jude Medical, and Medtronic have also developed or are developing their leadless pacing system. NDSU (<http://www.ndsuresearchfoundation.org>)¹³ has developed an innovative self-organizing, adaptive, wireless multi-electrode cardiac pacing system, where wireless electrodes communicate with each other and determine optimal heart stimulus pattern. Electrodes harvest energy from an externally placed can, which emits RF energy and can send commands to the electrodes. Sensors (micro electro-mechanical systems-MEMS accelerometers) embodied in each wireless electrode sense movement in the heart and communicate information to the network of connected electrodes. The electrodes work together to set an optimal pattern for stimulating regions of the heart to achieve an optimal cardiac output.

Nanostim (Milpitas, CA, USA)¹⁴ is also developing a miniaturized leadless pacemaker system for St. Jude Medical. Their primary battery uses beta-voltaic technology, promising a greater than 5-year longevity of the device. The company announced on 20/12/2012, the first successful implants of their leadless pacemaker in 11 patients in Prague, recruited in the LEADLESS study, conducted in 8 centers in Europe, and designed to examine the safety and effectiveness of a totally self-contained, leadless pacemaker system. Nanostim utilizes a catheter-based approach via the femoral vein delivering the leadless pacemaker directly into the RV.

Medtronic is also developing a leadless pacemaker. A miniaturized self-contained fully implantable pacing device working without pacing leads can be inserted via a catheter. Still in the research phase, Medtronic claims to have already created the majority of necessary components for the tiny pacemaker, including circuit board, oscillator, capacitor, memory, and wireless telemetry so that the device can communicate with external monitoring devices. The only thing missing is a power source. Some prototypes of miniscule pacing devices have already been announced and displayed at conferences (Figure). If eventually successful, pacemaker miniaturization will be a major accomplishment that can lower the risks & improve the benefits of pacing devices.

Conclusion

Although leadless pacing is indeed attractive and has the potential to reduce pacing complications, further development and clinical evidence of feasibility and efficacy will be required before it is clinically applied. However, these are complex systems and considerable technical difficulties, & bureaucratic obstacles will have

to be overcome for the ultrasound and other induction systems to be clinically viable. Self-powered contained, fully-implantable systems are more likely to become clinically useful if they have acceptable longevity, and if the device can be retrieved at the time of replacement.

For self-contained fully implantable systems, the most challenging engineering step seems to be power, which is a fundamental & crucial part of the pacemaker. Certainly there will need to be several studies to be conducted before the FDA could approve the miniature pacemaker for general use. It may be optimistic to estimate that the device could possibly be on the market in the next 5 years provided that engineering and regulatory demands have been fulfilled by then. Investigators are also working on MRI compatible leadless pacemaker devices.¹⁵



Figure. A self-contained miniature prototype of an active fixation leadless pacing device that is fully implantable via a steerable catheter delivery system (source: <http://spo.escardio.org/eslides/view.aspx?eevid=40&fp=318>)

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