

# In the Wireless Era: Leadless Pacing

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**LEE AND LAU: *In the Wireless Era: Leadless Pacing.*** Cardiac pacemakers have been the standard therapy for patients with bradyarrhythmias for several decades. The pacing lead is an integral part of the system that serves as a conduit for delivery of energy pulses to stimulate the myocardium. However, it is also an Achilles tendon that directly causes most device complications both acutely during implant and chronically years afterwards. Both durability and optimization of stimulation site are important areas of improvement for manufacturers and implanters. Elimination of the pacing lead and utilization of other means for energy transfer is the only way to avoid lead complications and allow better choice of stimulation site. Leadless pacing with ultrasound-mediated energy has been demonstrated in animals and humans in acute studies. This has aroused intense interest in the field of cardiac pacing. With concerted effort from the profession and the industry, leadless pacing may indeed become a sound idea. (*J HK Coll Cardiol* 2010;18:53-58)

*Cardiac resynchronization therapy, Heart failure, Pacemaker, Ultrasound*

## 摘要

過去的幾十年間，心臟起搏器已經成為治療有症狀的心動過緩患者一種標準的方法。而整體系統一部分的起搏器導聯，有著傳輸能量脈衝以刺激心臟的作用。然而無論是在起搏器植入後初期抑或是若干年後，有時仍會導致裝置相關的急慢性併發症。續航能力和刺激部位的適宜強度，無論對於製造商還是植入者而言，都是重要的關注點。去除起搏器的導聯，而運用其他方式進行能力傳輸是避免導聯相關併發症的唯一途徑，並且它為刺激部位提供更好的選擇。通過超聲介導能量的無導聯起搏器已經見諸與動物和人體的急性期研究中。這在心臟起搏器領域引起了強烈的關注。在醫學專業和製造專業的共同籌畫下，無導聯起搏器將會成為一個健全的構想。

關鍵詞：心臟再同步治療 心衰竭 起搏器 超聲波

## Introduction

All pacing leads are associated with complications like infection, fracture, failure and dislodgment. Lead extraction is a high risk procedure. With new device systems that often require implantation of multiple leads, and with patients living longer, the

incidence of lead complications becomes compounded over time.<sup>1</sup> Therefore, there is a strong demand to develop a pacing system that eliminates the pacing lead as a conduit for energy transfer. Randomized clinical trials on cardiac resynchronization therapy have demonstrated its clinical benefits. Access to the left ventricle is achieved with the use of a pacing lead to be advanced into the coronary sinus and positioned in a coronary vein branch. Implantation of this lead is technically demanding and associated with a significant incidence of failure to implant, implantation in a suboptimal location, and complications.<sup>2,3</sup> Comparing to epicardial pacing, endocardial left ventricular stimulation that minimizes the conduction delay from the epicardium to the endocardium may be more physiological and therefore give rise to greater

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hemodynamic benefits.<sup>4,5</sup> Leadless pacing will enable endocardial left ventricular stimulation without the risks of systemic thromboembolism and mitral regurgitation. It will also avoid diaphragmatic stimulation, avoid right ventricular apical pacing, enable multi-site pacing, and allow almost free choice of stimulation location within the left or right ventricle. It may also address challenges in pediatric pacing, and development of a truly MRI-compatible pacing system.

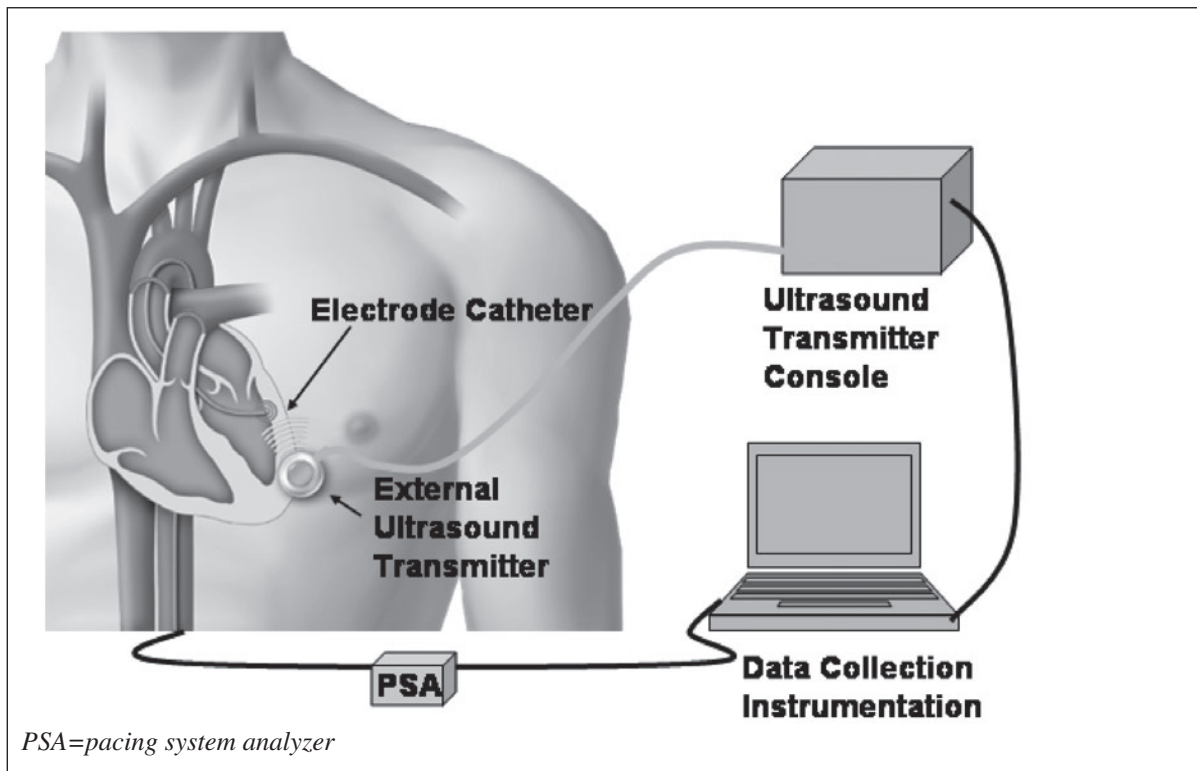
### Acoustic Energy for Leadless Pacing

Many concepts have been patented for the development of a leadless pacing system. Having a long history and wide application in medical technology, ultrasound energy is considered safe and was chosen to prove the concept of energy transfer. The use of ultrasound-mediated energy to drive a remotely positioned electrode for direct myocardial stimulation is the first to be reported in the medical literature. This new technology uses the mechanical-to-electrical properties of piezoelectric materials for transformation of energy. The experimental set-up include: an ultrasound transmitting transducer connected to an ultrasound generator, a steerable bipolar electrophysiology catheter incorporating a receiver-electrode at the distal tip. Ultrasound energy was amplitude-adjusted and transmitted at around 330 kHz. The lower frequency used in this application achieves better tissue penetration. Ultrasound pulses generated from the transmitting transducer traveled through the chest wall to reach the receiver-electrode with circuitry to transform the pulses into electrical energy for myocardial stimulation. The feasibility and safety of this novel technology was first demonstrated acutely in animals.<sup>6</sup> In the acute safety study, histological examination was performed in pigs that were exposed to continuous ultrasound transmission from the investigational system for two hours. No mechanical or thermal bio-effect was identified in the sacrificed animals. In the acute feasibility study, the receiver-electrode incorporated into a transvascular catheter was selective positioned and in contact with various heart chambers of a pig. An external transmitter was then

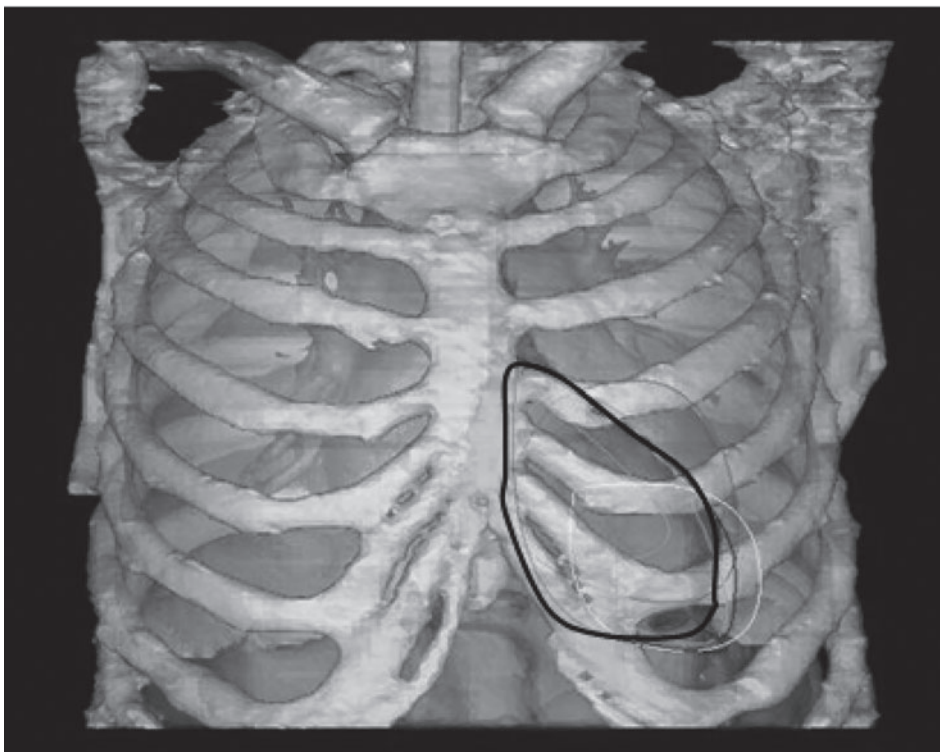
placed on the chest wall of the animal, with acoustic gel used for coupling. Ultrasound energy was then transmitted through the chest to the receiver, the acoustic energy was converted to electrical energy, and the electrodes contacting endocardium stimulated pacing. The electrode catheter was a modified steerable bipolar EP catheter with receiver-transducers incorporated near the tip between the bipolar pacing electrodes. Proximal connections on the catheter allowed either direct electrical pacing using a Pacing System Analyzer or monitoring of the receiver output during ultrasound-mediated pacing. The catheter itself was not directly involved in or required for ultrasound-mediated pacing. The acute porcine study demonstrated feasibility of leadless ultrasound-mediated pacing in five animals at 30 selected sites in the right atrium, right ventricle, left ventricle, and simultaneously in both left and right ventricles.<sup>6</sup>

Following the animal experiments, human studies were performed.<sup>7</sup> Twenty-four patients were tested during or after completion of clinical electrophysiology procedures (Figure 1). A total of 80 pacing sites in the right atrium, right ventricle, and left ventricle were tested. The transmit-to-receive distance was  $11.3 \pm 3.2$  cm. Ultrasound-mediated pacing was achieved at all 80 sites with consistent capture at 77 sites. There was no adverse event related to ultrasound-mediated pacing. No patient experienced discomfort during pacing. This novel technology targeting cardiac resynchronization therapy was also tested in heart failure patients.<sup>8</sup> In these patients, the acoustic window on the chest wall that allows efficient ultrasound transmission was defined and found to be large and sufficient for subcutaneous implantation of the ultrasound generator, even after accommodating changes with respiratory movement and body positioning (Figure 2).

Incorporating this novel technology, the future implantable leadless pacing system is being designed. The system includes an ultrasound generator to be implanted subcutaneously in the acoustic window of the chest wall and an endocardial receiver-electrode. The receiver electrode is delivered by a steerable transvascular catheter to the target heart chamber, and be detached and implanted onto the endocardium directly. The receiver and transmitter are programmed



**Figure 1.** Equipment set up of the first study of leadless pacing in humans.



**Figure 2.** Acoustic window outlined on a reconstruction CT thorax.

to operate at the same frequency of ultrasound pulses to avoid external interference. The ultrasound beam will be optimized and focused onto the receiver electrode in order to improve the efficacy of energy transfer. The estimated device longevity will need to be comparable to that of a conventional pacemaker to make it commercially viable. The acoustic window suitable for implant on the patient's chest wall can be localized preoperatively by conventional echocardiography, a convenient method that has been shown to predict efficient ultrasound transmission for leadless pacing.<sup>8</sup>

There are of course other unresolved issues that ongoing research is aiming to answer (Table 1).<sup>9,10</sup> For example, many will doubt the long term safety of continuous ultrasound exposure. Although the lack of effect of short term ultrasound-mediated pacing has been shown histologically in animal experiments, tissue injury secondary to heating with continuous exposure is theoretically possible. Similar studies on long term exposure when ultrasound energy was applied in continuous pacing will address the safety concern. Another challenge of this technology is environmental interference which may be ubiquitous. Although precise formatting and fine tuning of the device can be done, little is known about its actual performance in the real world. This is another big safety issue that requires extensive evaluation. Apart from energy delivery,

transmission of sensed endocardial electrograms is an important function of a pacing lead. There is so far no available information on how the sensing circuit of the future leadless pacemaker is going to operate. As for the risk of infection, the receiver electrode is small, embedded in the endocardial followed by complete endothelialization. It is expected to carry minimal risk of infection, probably comparable to that of coronary stents and atrial septal defect occluders.

### Alternative Energy Sources

Apart from ultrasound, an alternating magnetic energy source has been tested in a pig model for leadless cardiac stimulation.<sup>11</sup> The system consists of two components, an external transmitter unit and a receiver unit in contact with the myocardium. The subcutaneous primary coil generates an alternating magnetic field, which is converted by the secondary coil inside the heart to a voltage pulse for pacing stimulation. In the pig experiment described, an alternating magnetic field of approximately 0.5 mT was generated by the transmitter unit in a distance of 3 cm. Voltage pulses with a duration of 0.4 ms and voltage amplitude of 0.6-1.0 V were generated. Continuous stimulation of the heart was demonstrated for 30 minutes. The advantage of this

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**Table 1. Challenges in the development of leadless pacing technology**

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- Low efficiency of energy conversion significantly shortens battery longevity
  - Problem with consistent capture with a constantly changing pacing window
  - Long term safety of prolonged exposure to ultrasound with possible heating effect and tissue injury
  - Reliability of a leadless sensing circuit
  - Operation and integration of multiple sensing and pacing sites for CRT
  - Potential interference from external environment
  - Unconventional parasternal site for implanting the pacemaker generator
  - Development of a reliable delivery and anchoring system for implanting the endocardial receiver-electrode
  - Integration with an implantable defibrillator
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technology is that the efficiency of energy conversion is relatively high, making device longevity less of a problem. However, the transmitter coil is of considerable measurement, 60 mm in diameter, 10 mm in width, and 80 g in weight, while the receiver is 15 mm in length and 2.5 mm in diameter. Apart from the size of the device, one major concern of this technology is potential external interference by environmental magnetic fields. The long term safety with heat production in the receiver unit generated with continuous exposure is also uncertain.

Other wireless energy sources have been used for stimulation to a limited extent. Radiofrequency energy transmission is employed in an implantable micro-stimulator device currently under clinical investigation for neuro-modulation applications.<sup>12</sup> However, the implant incorporates a battery requiring frequent recharging using an inductive link from an external device. In general, the use of radiofrequency power for wireless applications in the body has the disadvantages of being unfocused and having a shallow depth of penetration. Therefore, it is less efficient than ultrasound energy. It also requires the transmitter and receiver to be in close proximity, which essentially precludes its use for many applications including cardiac pacing.

Ultrasound energy transduction is currently being used in a clinical application of a wireless sensor.<sup>13</sup> In this application, the receiver is coupled to a pressure transducer implanted within an abdominal aortic aneurysm graft for post procedure monitoring after endovascular repair. The transmitter is an external device placed on the anterior abdomen to communicate with the implanted receiver to acquire real time intrasac pressure data.

### Future Perspectives

Leadless pacing with ultrasound-mediated energy was demonstrated in animals and humans in acute studies. This is by far the most advanced development with proven technological feasibility. More scientific

data will be collected from ongoing animal and human research. With refinement of the technology, challenges identified will be addressed. Currently, a prototype device and the implantation equipment are being developed, and clinical trial of the permanent implantable system is being planned. At the same time, various competing technologies are being developed and evaluated. Although it is not certain if the intended progress will be accomplished, the favorable result achieved has aroused significant interest in the field of cardiac pacing. Many including those in the device industry are keen to be involved in the development of a commercially viable leadless implantable pacemaker. When this is materialized, lead complications and lead extractions will be minimized.

### Summary and Conclusions

Leadless pacing will also open up a new arena for cardiac resynchronization therapy. Some non-responders may be converted to responders with optimization of the left ventricular stimulation site. Multi-site pacing will no longer be limited by problems in vascular access or coronary venous anatomy. Responders may obtain maximal benefit from cardiac resynchronization therapy with endocardial left ventricular stimulation.

Although leadless pacing is only in the stage of proof-of-concept, subcutaneous implantable defibrillator has been developed and tested in clinical trial.<sup>14</sup> The preliminary result is encouraging. The integration of leadless pacemaker and subcutaneous implantable defibrillator is important as heart failure patients frequently require cardiac resynchronization therapy in combination with an implantable defibrillator.

Despite all the advances achieved, much more work needs to be done before we can accomplish this major breakthrough in the development of leadless implantable cardiac devices (Table 2). By that moment, implanting a pacing lead will become a procedure of history.



**Table 2. Key issues in development of leadless pacing**

- Pacemaker lead complications and failures are important clinical problems.
- The indication of device therapy has been expanded with the advent of cardiac resynchronization therapy; multiple pacing leads are now implanted in non-bradycardiac heart failure patients.
- Coronary vein anatomy may limit implant success and the clinical response to cardiac resynchronization therapy. The benefit of cardiac resynchronization therapy may be maximized with endocardial selected-site and multi-site pacing.
- The idea of energy transfer utilizing an external energy source to stimulate the heart directly was conceived as the basis of leadless pacing.
- Leadless cardiac stimulation with ultrasound-mediated energy was demonstrated to be feasible in acute studies in animal models, human patients and heart failure patients.
- Alternative technology of leadless cardiac stimulation with alternating magnetic field for energy induction has also been successful in an animal experiment.
- The future leadless pacemaker consists of a subcutaneously implanted ultrasound transmitter and an endocardially implanted receiver. A percutaneous catheter delivery and anchoring system will be used for the implantation procedure.
- The challenges of leadless pacing include but are not limited to the efficacy of energy conversion, potential external interference, sensing issues, and long term safety.
- A prototype device for leadless pacing with ultrasound energy has been developed for clinical testing. The first human implant may be feasible in the near future.

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