Journal of the American College of Cardiology
© 2007 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 50, No. 9, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.04.081

First Human Demonstration of Cardiac Stimulation With Transcutaneous Ultrasound Energy Delivery

Implications for Wireless Pacing With Implantable Devices

Kathy L. Lee, MBBS, FACC,* Chu-Pak Lau, MD, FACC,* Hung-Fat Tse, MD, FACC,* Debra S. Echt, MD, FACC,† David Heaven, MBChB,‡ Warren Smith, MBChB,‡ Margaret Hood, MBChB‡

Hong Kong SAR, China; Sunnyvale, California; and Auckland, New Zealand

Objectives The purpose of this study was to evaluate the feasibility and safety of a novel technology that uses energy transfer from an ultrasound transmitter to achieve cardiac stimulation without the use of a pacing lead in humans.

Background To overcome the limitations of pacemaker leads, a new technology enabling stimulation without the use of a lead is desirable.

Methods A steerable bipolar electrophysiology catheter incorporating a receiver electrode into the tip and circuitry to convert ultrasound energy to electrical energy was inserted transvenously into the heart. An ultrasound transmitting transducer was placed on the chest wall with ultrasound gel. Ultrasound energy was amplitude-adjusted and transmitted at 313 to 385 kHz. The output waveform of the receiver electrode was monitored while the transmitter was moved on the chest wall to target the receiver. The ultrasound transmission amplitude was limited to a mechanical index of 1.9, the maximum allowed for ultrasound imaging systems. Ultrasound-mediated pacing with minimum voltage but consistent capture was obtained for 12 s.

Results Twenty-four patients (48 ± 12 years) were tested during or after completion of clinical electrophysiology procedures. A total of 80 pacing sites were tested (mean 3.3 sites/patient): 12 right atrial, 35 right ventricular, and 33 left ventricular (31 endocardial) sites. The transmit-to-receive distance was 11.3 ± 3.2 cm (range 5.3 to 22.5 cm). Ultrasound-mediated pacing was achieved at all 80 test sites, with consistent capture at 77 sites. The mechanical index during pacing was 0.5 ± 0.3 (range 0.1 to 1.5). The mean ultrasound-mediated capture threshold was 1.01 ± 0.64 V. There was no adverse event related to ultrasound pacing. No patient experienced discomfort during pacing.

Conclusions The feasibility and safety of pacing usng ultrasound energy has been shown acutely. (J Am Coll Cardiol 2007; 50:877–83) © 2007 by the American College of Cardiology Foundation

Cardiac pacemakers have been the established therapy for patients with bradyarrhythmias for decades. Several recent findings have suggested a need for improving the standard transvenous leads used for permanent pacing. Firstly, clinical trials have indicated that conventional right ventricle (RV) apical pacing may be deleterious (1–5). This has led to the design and use of leads that can be implanted in other selected locations (6). Secondly, randomized clinical trials on cardiac resynchronization therapy (CRT) have shown its clinical benefits (7–9), especially when combined with an implantable cardioverter-defibrillator (10). However, approximately 30% of patients who received CRT did not have a response, due in part to an unfavorable left ventricular lead position (11,12). Access to the left ventricle (LV) for CRT is achieved with the use of a pacing lead advanced into the coronary sinus (CS) and positioned in a coronary vein (CV) 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 including perforation or dissection of the CS (13,14). Thirdly, all pacing leads are associated with complications such as infection, fracture, and dislodgment. Extraction of a failed lead that has been implanted for a long time is a high-risk procedure (15,16). With the new device systems that often require the implantation of multiple leads, and with patients living longer, the incidence of lead complications becomes compounded over time. Therefore,

From the *Cardiology Division, Department of Medicine, University of Hong Kong, Hong Kong SAR, China; †EBR Systems, Inc., Sunnyvale, California; and the ‡Cardiology Division, Greenlane Cardiovascular Service, Auckland City Hospital, Auckland, New Zealand. Supported by a research grant from EBR Systems, Inc. Dr. Echt is employed by EBR Systems, Inc.

Manuscript received October 16, 2006; revised manuscript received March 22, 2007, accepted April 18, 2007.

JACC Vol. 50, No. 9, 2007
August 28, 2007:877–83

Abbreviations and Acronyms

CPK = creatine phosphokinase
CRT = cardiac resynchronization therapy
CS = coronary sinus
CV = coronary vein
ECG = electrocardiogram
ISPPA = spatial peak pulse average intensity
ISPTA = spatial peak temporal average intensity
LV = left ventricle
MI = mechanical index
RA = right atrium
RV = right ventricle
TI = thermal index

there is a clinical need to develop a pacing system that reduces the problems inherent with the pacing leads. This study evaluates the feasibility of a novel technology that uses energy transfer from an ultrasound transmitter to a receiver electrode to achieve cardiac stimulation without the use of a pacing lead.

Methods

Patients. This 2-center study complied with the provisions of the Declaration of Helsinki, and was approved by the Institutional Review Board of the University of Hong Kong and the Northern X Regional Ethics Committee administered by the New Zealand Ministry of Health. The study was conducted as a nonrandomized prospective feasibility study in patients undergoing a clinical electrophysiology study for standard diagnostic and/or therapeutic indications. Patients who were 18 years or older and signed informed consent were eligible to participate. Patients with any of the following conditions were excluded: pregnancy, bacteremia, sepsis, active systemic infection, myocardial infarction within 2 weeks, cardiac surgery within 2 weeks, percutaneous coronary intervention within 2 weeks, unstable angina, acute myocardial ischemia, intracardiac thrombus, severe valvular heart disease, or clinical status unfit to undergo 30 to 60 min of additional testing.

Study equipment. The investigational stimulation system (EBR Systems, Inc., Sunnyvale, California) consisted of the following: 1) an ultrasound generator with an externally applied ultrasound transmission transducer; 2) a catheter incorporating a receiver electrode into the distal tip; and 3) a data collection and display system that included an electrophysiology recording system and a special instrument to monitor and record electrical data for ultrasound transmission and electrode output (Fig. 1).

The ultrasound generator and external transmitter produced a timed ultrasound field, coupled to the external surface/chest of the patient using coupling gel (Intelect, Chatanooga Corp., Chattanooga, Tennessee), and optionally a gel pad (Aquaflex, Parker Laboratories, Fairfield, New Jersey). The transmitter was similar in appearance and function to an ultrasound imaging wand. The catheter containing the receiver electrode was a custom 6-F steerable electrophysiology catheter (EBR Systems, Inc.). The receiving transducer and circuitry converted ultrasound energy to electrical energy and output the electrical energy to a pair of bipolar electrodes. The cathode electrode was a 4-mm-long hemispherical platinum/iridium electrode located at the tip,

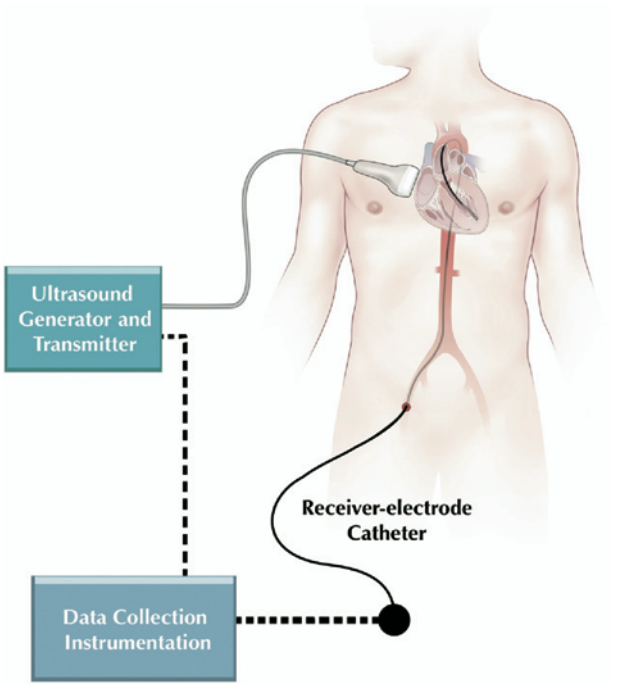

Figure 1 **Investigational Device System**

Diagram of the investigational device system consisting of an ultrasound generator with an externally applied ultrasound transmit transducer, an intracardiac catheter containing a receiver electrode incorporated into the distal tip, and data collection instrumentation including an electrophysiology recording system and storage oscilloscopes.

and the anode was a 2-mm-long ring platinum/iridium electrode located 1 cm proximally. Transmitted ultrasound waves passed into and through the patient's body and intersected the receiver. The circuitry connected to the receiver converted the ultrasound waveform to an electrical square wave output delivered between the bipolar electrodes to stimulate/pace the heart.

The ultrasound generator had a display screen and control buttons to provide adjustable settings for ultrasound transmission frequency, amplitude, transmit burst duration (pulse width), and transmit interval (cycle length). The ultrasound transmission frequency to be used was optimally adjusted for each receiver electrode. The frequency selected was determined based on water tank calibration testing during catheter construction. Selection of the ultrasound transmission amplitude was limited to an output corresponding to a mechanical index (MI) of 1.9 in the heart. This limit was selected because it is the maximum amplitude typically used for ultrasound imaging systems.

Connections to the distal and proximal electrodes were available in the catheter handle to allow for connection to an electrical pacing stimulator, an electrophysiology laboratory recording system (Maclab, GE Healthcare, Waukesha, Wisconsin; EP MedSystems, West Berlin, New Jersey), or instrumentation for monitoring of the electrical output

voltages on the electrodes during ultrasound-medicated pacing (Tektronix TDS 3014B, Beaverton, Oregon). Electrical pacing was accomplished using a standard programmed stimulator (EP MedSystems). Recordings of intracardiac electrograms during intrinsic rhythms and that of surface electrocardiogram (ECG) during electrical pacing and ultrasound-mediated pacing were obtained.

The receiver electrode output voltage was monitored in real time on 2 patient-isolated oscilloscopes; 1 was used to assist the operator of the transmitter on the chest wall in the targeting of the receiver, and the other was used for data collection. The ultrasound generator was also connected to the oscilloscopes to monitor ultrasound transmission.

Study protocol. Prestudy safety procedures included a complete cardiovascular examination, a 12-lead ECG, serum creatine phosphokinase (CPK) with MB isoenzyme level, and a transthoracic echocardiogram to assess for intracardiac thrombus, valvular disease, pericardial effusion, or other abnormalities. After completion of the prestudy procedures, patients underwent testing in the clinical electrophysiology laboratory, either during or after completion of the clinical electrophysiology procedure. The receiver electrode catheter was introduced through the femoral vein and positioned in right atrium (RA), RV, or CV sites for both electrical and ultrasound-mediated pacing. In patients who needed mapping of the left heart, the catheter was positioned in the endocardial LV sites by antegrade transeptal or retrograde transaortic approach, and unfractionated heparin was used to maintain an activated clotting time of 200 to 300 s throughout the procedure. The selection of stimulation sites for testing was at the discretion of the attending physician.

The testing sequence for each site was as follows. The intracardiac electrograms from the catheter electrodes were recorded to confirm contact with viable myocardium. The electrical pacing threshold was obtained at a pacing cycle length approximately 20% below the inherent cycle length at 0.5-ms pulse width. Twelve seconds of consistent capture was recorded for documentation. The catheter electrodes were then connected to the oscilloscopes to monitor the voltage output during ultrasound-mediated pacing. The ultrasound transmitter was placed on an optimal position on the chest wall. Pacing was accomplished by transcutaneous ultrasound bursts transmitted at the identical pacing cycle length and pulse width used for electrical pacing. Twelve seconds of consistent capture was recorded for documentation. After the initial 6 patients, the ultrasound-mediated pacing threshold was also determined. The patients were queried regarding any auditory or tactile sensations experienced during ultrasound transmission. The location of the transmitter was noted, and the location of the receiver electrode was recorded on cine images. The catheter was repositioned to another site, and the testing sequence was repeated.

After the study protocol, patients underwent postprocedure safety testing identical to that performed before the procedure and were assessed for potential adverse events.

Data analysis. The primary study efficacy end point was ECG-documented stable ultrasound-mediated pacing at the RA, RV, and LV sites at which consistent electrical pacing was achieved. The primary safety end point was freedom from investigational device-related adverse events. Triggered oscilloscope recordings of 12 s of ultrasound-mediated pacing were analyzed for the minimum and the maximum output voltages at the terminal portion of the pacing pulses. The minimum receiver electrode output voltage at the terminal portion of the pacing pulse was defined as the ultrasound-mediated pacing threshold. To directly compare the electrical pacing thresholds measured as current (mA) with the ultrasound-mediated pacing thresholds measured as voltage (V), a tissue impedance of 605 Ohms was used. This value was calculated using a model for pacing leads (17), with adjustments made based on preclinical experimental measurements. Distances from the transmitter to the receiver were calculated by measuring the oscilloscope recording time delay from the onset of the ultrasound transmission burst to the onset of the receiver electrode output, multiplied by the speed of sound through the tissue (1.5 mm/μs) (18). Based on preprocedure and postprocedure water tank calibration testing of the transmitter and receivers, and corrections for tissue attenuation and distance, the MI at the receiver was calculated for each pacing site. Two energy calculations were made, the ultrasound energy from the transmitter burst and the electrical energy output from the stimulation pulse.

Statistical analysis. Data are presented as mean ± SD. The Student paired *t* test was applied to compare electrical pacing thresholds and minimum receiver electrode voltages. A probability value <0.05 was considered statistically significant.

Results

Patient characteristics. Twenty-four patients, 12 male and 12 female, were evaluated with the investigational pacing system. The patients' ages were 48 ± 12 years and weight was 75.2 ± 15.7 kg (range 50 to 116 kg). The concurrent electrophysiology procedures performed were radiofrequency ablation for atrioventricular nodal re-entry tachycardia in 7 patients, atrioventricular re-entry tachycardia in 6 patients, atrial fibrillation in 2 patients, atrial flutter in 3 patients, ventricular tachycardia in 1 patient, both atrioventricular nodal re-entry and ventricular tachycardia in 1 patient, and 4 patients underwent diagnostic electrophysiology studies alone. One patient each had a history of aortic regurgitation, hypertrophic cardiomyopathy, heart failure, hypertension, coronary artery disease, and cerebrovascular accident. In the patient with heart failure, pre-existing atrioventricular conduction abnormality was present, and a dual-chamber pacemaker (Philos, Biotronik, Berlin, Germany) had been implanted. No other cardiovascular condition was present in 18 patients.

Overall results. A total of 82 sites in the RA, RV, and LV were evaluated with the investigational pacing system. Two sites were excluded for analysis because electrical pacing capture was inconsistent. Of the 80 sites analyzed, 12 were

JACC Vol. 50, No. 9, 2007
August 28, 2007:877–83

within the RA, 35 were within the RV, 31 were within the LV, and 2 were epicardial LV from the CV. A mean of 3.3 and range of 2 sites to 6 sites were evaluated per patient. Electrical and ultrasound-mediated pacing was performed at a 460- to 600-ms pacing cycle length and a 0.5-ms pulse width. Ultrasound was transmitted at a mean frequency of 350 ± 25 kHz, ranging from 313 to 385 kHz. A typical ultrasound waveform is shown in Figure 2, and a typical receiver electrode output waveform is shown in Figure 3. Ultrasound-mediated pacing was successful at all 80 sites with consistent pacing capture achieved at 77 sites. There was beat-to-beat variation in the receiver electrode output voltage during pacing, and it ranged from a minimum of 1.04 ± 0.67 V to a maximum of 2.16 ± 1.10 V. The ultrasound-mediated pacing threshold, attempted at 59 sites in 18 patients was 1.01 ± 0.64 V. The electrical pacing threshold, obtained at 70 sites in 21 patients, was 1.60 ± 1.12 mA. Assuming a tissue impedance of 605 Ohms, the electrical pacing threshold was 0.97 ± 0.67, similar to the ultrasound-mediated pacing threshold. The receiver electrode output waveform from a storage oscilloscope is shown in Figure 4. The MI at the site during ultrasound-mediated pacing was calculated to be 0.51 ± 0.31 MI, ranging from 0.12 to 1.50 MI. In the 18 patients in whom ultrasound-mediated pacing thresholds were obtained, the MI at the site was calculated to be 0.45 ± 0.30 MI. The mean electrical output energy per pacing pulse was 2.68 ± 3.04 μJ, whereas the mean ultrasound energy burst was 12.86 ± 15.70 mJ. Figures 5A and 5B are examples of electrical and ultrasound-mediated pacing from a midlateral LV site showing that ECG morphology and blood pressure were identical. The results of pacing capture in each chamber are shown in Table 1.

Anatomical considerations. Figure 6 shows 3 diagrams of the human torso, with a 3 × 3 grid in which each square is 2 inches, superimposed over the chest wall region. Grids labeled A, D, and G were centered over the sternum. As indicated by dots, the most commonly used chest location for ultrasound transmission was within grid E or on the border of grids D and E. This corresponded to the left parasternal region at the fifth intercostal space. However, not infrequently the transmitter position was directly over the fourth rib, in the fourth intercostals space, or on the sternum. The transmitter was angled up to 45° superiorly from perpendicular to target right-sided sites and up to 20° to the left to target LV sites. The mean transmit-to-receive

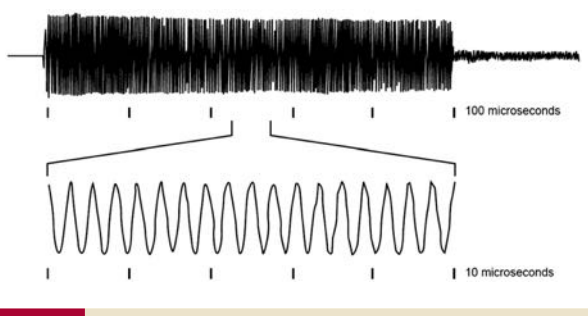

Figure 2 Ultrasound Burst

Recording of an ultrasound burst delivery at a frequency of 350 kHz and a burst duration of 0.5 ms.

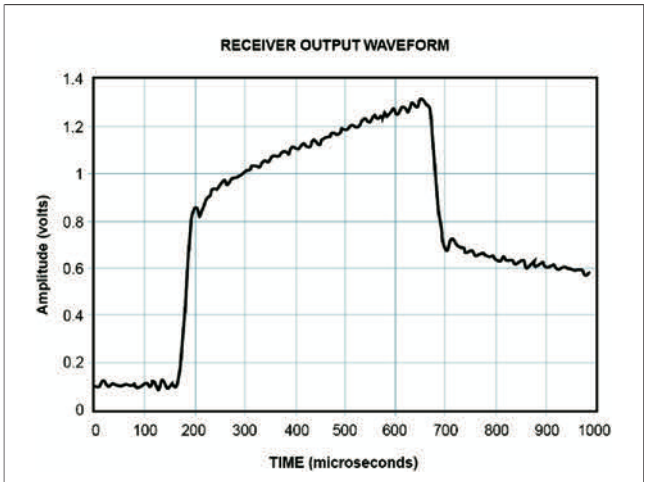

Figure 3 Waveform Recording

Recording of a receiver electrode output waveform taken from a posteroseptal right ventricular site. The voltage is 0.825 V at the leading edge and 1.29 V at the trailing edge, and the pulse width is 0.5 ms.

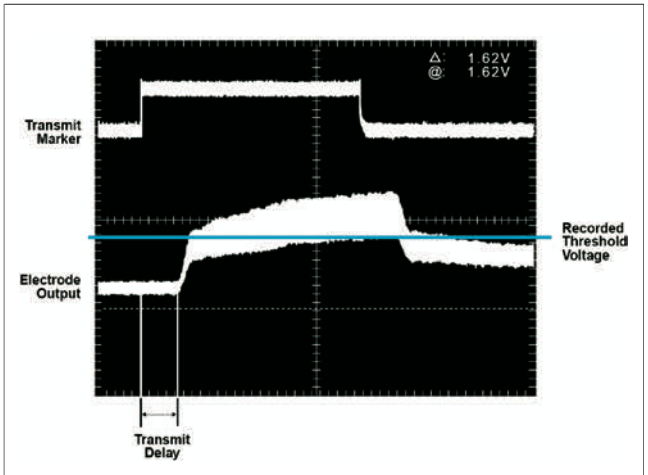

Figure 4 Ultrasound-Mediated Pacing Threshold

Recording of the storage oscilloscope monitoring the receiver electrode output capturing 12 s of ultrasound delivery in triggered mode. The **top trace** depicts the ultrasound transmit marker and duration of 0.5 ms. The **bottom trace** depicts 12 s of electrode output waveforms (20 superimposed waveforms). Beat-to-beat variation in output voltage resulted in the appearance of a wide band. The minimal voltage, recorded as the ultrasound-mediated pacing threshold voltage, was measured at the lower boundary of the trailing edge of the superimposed output waveforms. The maximum voltage was measured at the upper boundary of the trailing edge of the superimposed output waveforms. The transmitter-to-receiver distance was calculated from the transmit delay from the onset of the ultrasound transmission to the onset of the electrode output waveform.

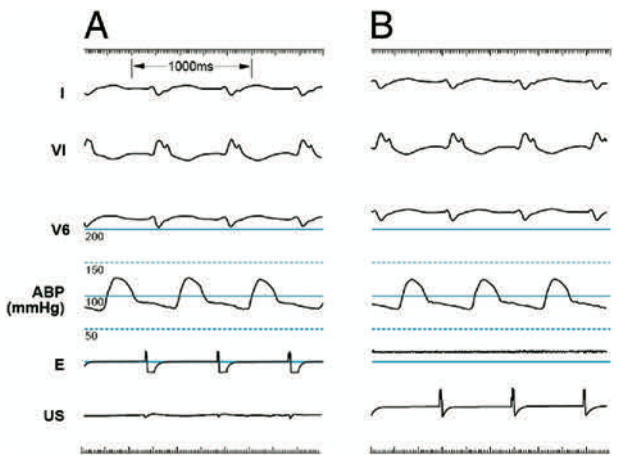

Figure 5 **Ultrasound and Electrical Stimulation**

Recordings obtained by the investigational catheter positioned at a midlateral left ventricular site during **(A)** electrical pacing and **(B)** ultrasound-mediated pacing. Tracing shown from top to bottom are surface electrocardiogram (ECG) lead I, V_1, V_6, aortic blood pressure (ABP), electrical stimulation (E), and ultrasound transmission (US) marker channels.

distance was 11.3 ± 3.2 cm, ranging from 5.3 to 22.5 cm. This measurement included traversing the 1-cm-thick gel pad used for 39 of 80 sites to facilitate angulation of the transmitter. If the contribution of the gel pad thickness to the distance measurements were eliminated, the mean transmit-to-receive distance was 10.7 ± 3.08 cm.

The general locations of the pacing sites and pacing data for sites in each of the RA, RV, and LV chambers are listed in Table 1. Results for each heart chamber were similar except that the distances to the RV sites were generally shorter than those to the RA and LV sites. The MI for ultrasound-mediated pacing tended to be higher in the RA, and the mean energy efficiency tended to be lower. The apparent higher electrical pacing threshold in the LV is attributed to the 2 epicardial sites accessed from the CS, which were 7 and 5 mA. There were 3 sites in which ultrasound-mediated pacing was inconsistent, 2 were in the RA on the lateral wall and 1 was an epicardial LV site in the posterior CV.

Safety results. The results of safety testing performed before and after the research protocol did not reveal any abnormality attributable to the investigational devices. One patient experienced a procedure-related adverse event of a false aneurysm of the femoral artery that was treated successfully with thrombin injection. Nine patients had expected minimal elevations of CPK and creatine kinase-MB level attributable to the concomitant clinical ablation procedure. No patient experienced discomfort during ultrasound-mediated pacing. Only 1 patient noted a very mild pressure sensation for 1 of 4 sites tested.

In addition to MI values, thermal index (TI) values and standard ultrasound indices of intensity, spatial peak pulse average intensity (ISPPA), and spatial peak temporal average intensity (ISPTA) were calculated. The average peak TI, located 2.5 to 3.0 cm from the transmitter surface, was 0.0326 (range 0.001 to 0.144) for soft tissue and 0.855 (range 0.03 to 4.14) for bone. The average ISPPA was 22.7 W/cm^2 (range 0.74 to 112 W/cm^2), and the average ISPTA was 19.23 mW/cm^2 (range 0.62 to 93.1 mW/cm^2). Both parameters were well below the FDA preamendment diagnostic ultrasound acoustic output intensity guideline recommendations that ISPPA should not exceed 190 W/cm^2 and ISPTA should not exceed 430 mW/cm^2 (19).

Discussion

To the best of our knowledge, this is the first demonstration in humans of using energy transfer to achieve cardiac stimulation without the use of leads. Acute success of this novel technology using ultrasound energy transmission through the body provides evidence for the feasibility of developing implantable cardiac pacemaker systems without pacing leads.

Safety considerations. To assess safety before performing this study in patients, preclinical studies were performed in

Table 1 **Electrical and Ultrasound Pacing Parameters of All Cardiac Chambers Evaluated**

Cardiac Chambers	Right Atrium		Right Ventricle		Left Ventricle		All	
Number of sites and receiver locations	12	High septum (5) Low septum (3) Lateral (3) Appendage (1)	35	Apex (12) Outflow tract (9) Septum (6) Posterior (4) Anterior (2) Lateral (2)	33	Endocardial: Lateral (15) Posterior (11) Septum (4) Apex (1) Epicardial: Posterior (2)	80	All
Electrical pacing threshold (V)*	12	0.83 ± 0.16	31	0.81 ± 0.51	27	1.22 ± 0.89	70	0.970 ± 0.67
Minimum receiver electrode output (V)	5	0.66 ± 0.21†	26	1.00 ± 0.47†	27	1.08 ± 0.80†	59	1.01 ± 0.64†
Maximum receiver electrode output (V)	12	1.95 ± 0.65	35	2.17 ± 0.96	33	2.23 ± 1.35	80	2.16 ± 1.10
Mechanical index	12	0.72 ± 0.23	35	0.51 ± 0.32	33	0.46 ± 0.28	80	0.51 ± 0.31
Transmitter-to-receiver distance (cm)	12	13.8 ± 1.8	35	8.5 ± 1.9	33	13.1 ± 2.3	80	11.3 ± 3.2
Electrical output energy per pacing pulse (μJ)	12	1.50 ± 0.81	35	2.63 ± 2.22	33	3.11 ± 4.06	80	2.68 ± 3.04
Ultrasound output energy per transmit burst (mJ)	12	26.60 ± 17.36	35	7.29 ± 9.26	33	14.19 ± 7.74	80	12.86 ± 15.70

*Assumes impedance of 605 Ohms. Values in remainder of table are presented as n, mean ± SD. †p = NS (paired *t* test) comparing electrical pacing voltage threshold and minimum receiver electrode voltage.

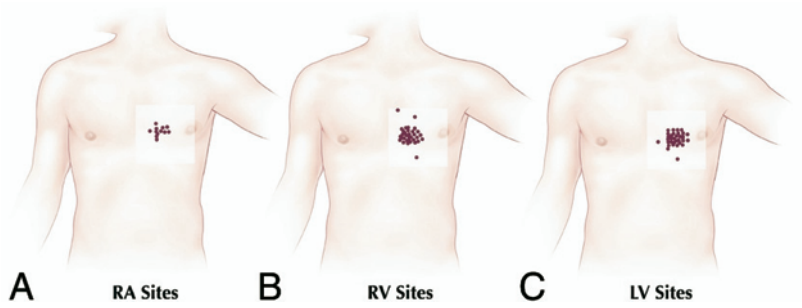

Figure 6 **Ultrasound Window**

Drawings of the human torso with a grid representing the window used for transmission of ultrasound energy over the chest wall. The central position of the transmitter targeting a site in the **(A)** RA, **(B)** RV, and **(C)** LV is shown as a **dot**. LV = left ventricle; RA = right atrium; RV = right ventricle.

6 animals (5 treated and 1 sham) (20). Ultrasound energy was applied at intensities and durations anticipated to exceed those used in human testing. Histopathological evaluation performed from specimens of the heart, lungs, and chest wall showed no evidence of bioeffects attributable to ultrasound transmission.

Technical advantages. The use of ultrasound energy provides several advantages over other forms of remote energy transfer. For example, conventional pacemakers are vulnerable to interference from the use of electromagnetic energy sources but not ultrasound transmission. One of our study patients was pacing-dependent, and pacemaker function during transmission of ultrasound energy was normal.

At the lower ultrasound frequencies used in this study, in the range of 350 kHz, there is relatively little attenuation over distance. Water tank bench testing showed no significant change in ultrasound intensities at the range of distances encountered in this study. Consistent pacing was achieved at various transmission distances of up to 22.5 cm. This is in contrast to the ultrasound frequencies used for transthoracic ultrasound imaging or intracardiac ultrasound imaging applications, using the frequency range of 2 to 5 MHz or 25 to 30 MHz correspondingly, where attenuation limits beam penetration to within approximately 10 or 1 cm respectively. The lower frequencies used in this study also enable penetration through bone with only minor attenuation of about 3 dB (18), which enlarges the area of the transthoracic ultrasound window. This allows better design of the transducer that improves the efficiency of energy conversion by enhancing the focus of the ultrasound beam.

Technical challenges. Ultrasound-mediated cardiac stimulation was shown at all 80 sites tested, and consistent pacing was shown in 77 sites. The inability to pace consistently at 3 sites is partly attributable to the protocol limitation of a maximum MI. This restriction was imposed to voluntarily conform to levels used for commercial ultrasound imaging systems (19). It is likely that higher ultrasound amplitudes would have resulted in consistent capture at these sites. Another issue was substantial beat-to-beat variation observed in the receiver electrode output. As shown in Table 1 and Figure 4, the receiver electrode output maximum voltages averaged 2-fold higher than the minimum voltages. For the 3 sites with inconsistent pacing, pacing capture only occurred on beats having receiver electrode output voltages above the minimum voltage. Consistent pacing, therefore, was achievable only if all stimulation pulses were above the minimum receiver electrode output voltage threshold. Several factors contribute to the beat-to-beat variability in output voltages. One factor is that ultrasound energy in the transmitted beam in the direct path of the lungs is reflected, some into the direct path of the receivers. Depending on phase shifts, the receiver electrode output amplitude at any point in time may be enhanced or reduced. This phenomena can be identified both by amplitude variations within an individual receiver electrode output waveform pulse as well as between pulses. Because the velocity of sound in bone is different from that in other tissue, there are also refractive effects from the ribs. Other factors include variations caused by cardiac and respiratory motion, and to a lesser extent in this protocol, to body movement and position. The angle of the receiver in relationship to the angle of the transmitted ultrasound beam varied with motion, causing further variation in energy reception depending on the angulation during the ultrasound pulse. Also, the ultrasound beam profile is not completely homogeneous across the beam. Finally, attenuation of the ultrasound beam is known to occur with distance because of tissue absorption. For all of these reasons, the receiver may be exposed to differing amplitudes of ultrasound energy during the pacing attempts. A focus of future studies will be to elucidate the mechanisms of beat-to-beat variability.

This new technology is associated with inherent inefficiencies as compared with direct electrical stimulation. The efficiency of energy conversion, as calculated from the receiver electrode output energy compared with the transmitted energy (Table 1), was only 0.063%. No attempt was made to optimize the energy efficiency of the system used in

these studies. Electrical energy is expended to initially generate the ultrasound transmission, ultrasound energy disperses across its beam, the ultrasound energy attenuates over distance because of absorption into tissue, and finally the energy must be transduced back into electrical energy for pacing. There are opportunities for substantial improvement in these areas, especially the transmitter beam. The transmitter beam used in the study was broad and unfocused; the receiver area was only 0.0045% of the beam area. Dynamic focusing of the beam could markedly increase efficiency. With today's battery technology and optimization in this ultrasound system, it is likely that a single-chamber pacemaker with reasonable longevity is feasible.

Study limitations. The majority of the patients had structurally normal hearts. There would likely be differences in results in patients with a dilated heart and abnormal cardiac anatomy. Patients were tested in the supine position only. The effects caused by cardiac contraction and respiration motion were observed, but those caused by changes in body position were not evaluated. Because pacing was evaluated acutely, the conclusions cannot be extrapolated to the extended period of pacing.

Future applications. The technology tested acutely in this study is currently under development as a leadless implantable system for chronic clinical use. It will be composed of an ultrasound pulse generator, receiver electrode(s), delivery catheter(s), and programmer/pacing system analyzer. The implantation of a relatively small receiver electrode in the heart will entail the percutaneous insertion of a preloaded delivery catheter via a femoral artery or vein. The delivery catheter will be advanced to a selected endocardial site. The receiver electrode will be activated to assess pacing from that site, and the receiver electrode will be deployed by active fixation for implantation. The pulse generator device will include an ultrasound transmitter, cardiac signal processing circuits, pacing control logic, and a battery. It will be implanted subcutaneously in the left precordial chest region. The precordial location will be selected to optimize ultrasound energy transmission to the implanted receiver(s). The programmer/pacing system analyzer will provide tools for pacing assessment for implant procedure and follow-up.

Conclusions

The feasibility and safety of cardiac stimulation using a remote energy source, without pain or discomfort, has been shown in the short term in patients for the first time. This new technology using ultrasound energy has the potential for application to permanent pacing systems. It has the advantages of avoiding the complications inherent to pacing leads and accessibility to different locations within various cardiac chambers enabling selective-site and multisite pacing. The development of implantable receiver electrodes holds hope for a new paradigm in pacemaker therapy.

Reprint requests and correspondence: Dr. Kathy L. Lee, Cardiology Division, Department of Medicine, Queen Mary Hospital, 102, Pokfulam Road, Hong Kong SAR, China. E-mail: klflee@hku.hk.

REFERENCES

1. Toff WD, Skehan JD, DeBono DP, Camm AJ. The United Kingdom pacing and cardiovascular events (UKPACE) trial. Heart 1997;78:221–3.
2. Lamas GA, Orav EJ, Stambler BS, et al., for the PASE Investigators. Quality of life and clinical outcomes in elderly patients treated with ventricular pacing as compared with dual-chamber pacing. N Engl J Med 1998;338:1097–104.
3. Skanes AC, Krahn AD, Yee R, et al., for the CTOPP Investigators. Progression to chronic atrial fibrillation after pacing: the Canadian trial of physiologic pacing. J Am Coll Cardiol 2001;38:167–72.
4. Sharma AD, Rizo-Patron C, Hallstrom AP, et al., for the DAVID Investigators. Percent right ventricular pacing predicts outcomes in the DAVID trial. Heart Rhythm 2005;2:830–4.
5. Sweeney MO, Hellkamp AS, Ellengogen KA, et al., for the MOST Investigators. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation 2003;107:2932–7.
6. Lieberman R, Grenz D, Mond HG, Gammage MD. Selective site pacing: defining and reaching the selected site. Pacing Clin Electrophysiol 2004;27:883–6.
7. Auricchio A, Abraham WT. Cardiac resynchronization therapy: current state of the art. Circulation 2004;109:300–7.
8. Saxon LA, Ellengogen KA. Resynchronization therapy for the treatment of heart failure. Circulation 2003;108:1044–8.
9. Cleland JGF, Daubert J, Erdmann E, et al., for the CARE-HF Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1–11.
10. Bristow MR, Saxon LA, Boehmer J, et al., for the COMPANION Investigators. Cardiac resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140–50.
11. Stevenson LW. The points for pacing. J Am Coll Cardiol 2003;42:1460–2.
12. Pitzalis MV, Iacoviello M, Romito R, et al. Ventricular asynchrony predicts a better outcome in patients with chronic heart failure receiving cardiac resynchronization therapy. J Am Coll Cardiol 2005;45:65–9.
13. Bax JJ, Abraham T, Barold SS, et al. Cardiac resynchronization therapy. Part 2—Issues during and after device implantation and unresolved questions. J Am Coll Cardiol 2005;46:2168–84.
14. McAlister FA, Ezekowitz JA, Wiebe N, et al. Systematic review: cardiac resynchronization in patients with symptomatic heart failure. Ann Int Med 2004;141:381–90.
15. Verma A, Wilkoff BL. Intravascular pacemaker and defibrillator lead extraction: a state-of-the-art review. Heart Rhythm 2004;1:739–45.
16. Kutalek SP. Pacemaker and defibrillator lead extraction. Curr Opin Cardiol 2003;19:19–22.
17. Soykan O. Automated piecewise linear modeling of pacing leads. Proceedings of the 16th Annual International Conference of the IEEE. Piscataway, NJ: IEEE Publishing, 1994;1:53–4.
18. Wells PNT. Velocity, absorption and attenuation in biological material. In: Biomedical Ultrasonics. London: Academic, 1977:110–37.
19. Food and Drug Administration. Information for Manufacturers Seeking Marketing Clearance of Diagnostic Ultrasound Systems and Transducers. Rockville, MD: U.S. Department of Health and Human Services, Center for Devices and Radiological Health, 1997.
20. Echt DS, Cowan MW, Riley RE, Brisken AF. Feasibility and safety of a novel technology for pacing without leads. Heart Rhythm 2006;10:1202–6.