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Permanent Leadless Cardiac Pacing
Results of the LEADLESS Trial

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Background—Conventional cardiac pacemakers are associated with several potential short- and long-term complications related to either the transvenous lead or subcutaneous pulse generator. We tested the safety and clinical performance of a novel, completely self-contained leadless cardiac pacemaker.

Methods and Results—The primary safety end point was freedom from complications at 90 days. Secondary performance end points included implant success rate, implant time, and measures of device performance (pacing/sensing thresholds and rate-responsive performance). The mean age of the patient cohort (n=33) was 77±8 years, and 67% of the patients were male (n=22/33). The most common indication for cardiac pacing was permanent atrial fibrillation with atrioventricular block (n=22, 67%). The implant success rate was 97% (n=32). Five patients (15%) required the use of >1 leadless cardiac pacemaker during the procedure. One patient developed right ventricular perforation and cardiac tamponade during the implant procedure, and eventually died as the result of a stroke. The overall complication-free rate was 94% (31/33). After 3 months of follow-up, the measures of pacing performance (sensing, impedance, and pacing threshold) either improved or were stable within the accepted range.

Conclusions—In a prospective nonrandomized study, a completely self-contained, single-chamber leadless cardiac pacemaker has shown to be safe and feasible. The absence of a transvenous lead and subcutaneous pulse generator could represent a paradigm shift in cardiac pacing.

Clinical Trial Registration—URL: http://clinicaltrials.gov. Unique identifier: NCT01700244.

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Key Words: pacemaker, cardiac

Nearly 250 000 new cardiac pacemakers are implanted annually in the United States, and an additional 750 000 are implanted worldwide.[1] Although transvenous cardiac pacemakers improve quality of life and reduce mortality in at-risk patients, they are associated with several potential procedure- and device-related complications. Approximately 10% of patients experience a short-term complication related to transvenous implantation of the pacemaker.[2] These may be attributable to either the pulse generator (hematoma, skin breakdown, pocket infection) or venous access and lead implantation (pneumothorax, cardiac tamponade, lead dislodgement).[2] In the long term, transvenous leads, often considered the weakest link of the cardiac pacing system, can potentiate venous obstruction and are prone to insulation breaks, conductor fracture, and infection.[2–4] Aside from the acquired comorbidities that can accompany these complications of conventional cardiac pacing systems, there are also significant incremental costs associated with each of these untoward outcomes.[5] Although it has been >40 years since the conception of a totally self-contained cardiac pacemaker, until now there have not been any implants in humans.[6,7] Herein, we present the safety and clinical performance of a novel, completely self-contained leadless cardiac pacemaker (LCP) in 33 patients.

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Methods

Study Design

LEADLESS is a prospective, nonrandomized, single-arm multicenter study of the safety and clinical performance of a completely

self-contained leadless cardiac pacemaker. Thirty-three patients underwent implantation of the LCP and were followed for 90 days. Patients with a clinical indication for single-chamber (right ventricular) pacing (VVIR) were eligible for the device. Indications included (1) permanent atrial fibrillation (AF) with atrioventricular (AV) block (which includes AF with a slow ventricular response), (2) normal sinus rhythm with second or third degree AV block with a low level of physical activity or short expected lifespan, or (3) sinus bradycardia with infrequent pauses or unexplained syncope with electrophysiology findings (eg, prolonged HV interval).[8] Patients were excluded if they were pacemaker dependent, had a mechanical tricuspid valve prosthesis, had pulmonary hypertension, preexisting pacemaker/defibrillator leads, or an inferior vena cava filter. Follow-up assessments were performed predischarge and at 2, 6, and 12 weeks postimplantation. At the 2-week follow-up visit, capable patients underwent a 6-minute walk test, with the device programmed to VVIR (rate-responsive) calibration mode.[9] The implanting physicians were provided with the results of this examination, and the programming of the device (ie, rate response on or off) was left to their discretion. Patients were enrolled after written informed consent. The devices were implanted in the patients between December 2012 and April 2013 in the 3 participating centers. The local institutional review board for each participating center approved the study (clinicaltrials.gov, NCT01700244).

Safety End Points

The primary safety end point was freedom from complications (complication-free rate), defined as serious adverse device effects at 90 days. Safety was measured by reporting the complication-free rate, based on subjects who complete their 90-day follow-up visit or drop out because of a complication. The secondary safety end point was implant success rate, defined as the percentage of subjects leaving the implant procedure with an implanted and functioning LCP device. The secondary performance end points were pacemaker performance characteristics (descriptive statistics) including pacing threshold, pacing impedance, cell voltage, R-wave amplitude, pacing percentage, and cumulative cell charge. Additionally, the LCP performance was assessed during magnet testing (predischarge) and 6-minute walk tests (at the 2-week visit if the patient was physically capable). An independent data and safety monitoring board reviewed the safety and performance data.

LCP Details and Implantation

The LCP (Nanostim Inc, Sunnyvale CA) is an entirely self-contained intracardiac device that includes the pacemaker electronics, lithium battery, and electrodes (Figure 1). The LCP length is 42 mm with a maximum diameter of 5.99 mm. A distal nonretractable, single-turn (screw-in) steroid-eluting (dexamethasone sodium phosphate) helix affixes the LCP to the endocardium. The maximum depth of penetration of the fixation mechanism in tissue is 1.3 mm. Sensing, pacing, and communication with the external programmer occur between a distal electrode near the helix and the external can of the LCP. The tip electrode is located at the center of the fixation helix. The ring electrode is the uncoated part of the titanium pacemaker case, and the interelectrode distance is >10 mm. The pacemaker's proximal end has a feature for docking the delivery and retrieval catheters.

After placing a 30-cm 18F sheath in the femoral vein (most commonly, the right femoral vein), the device is delivered to the right ventricle (RV) with the use of a deflectable delivery catheter with an extendable sleeve to protect the fixation helix (Figure 2). Once positioned, the sleeve is retracted, and the device is implanted into the endocardium (rotation affixes the helix) and then undocked from the delivery catheter while a tethered connection is maintained to permit device measurements and assess stability without the force of the catheter on the LCP. If the position is suboptimal, the LCP can be reengaged, unscrewed, and repositioned. The system also includes single- or triple-loop snare retrieval catheters that can engage the LCP docking feature for retrieval once the device is fully deployed. Figure 3 is an example of a chest x-ray of the final implant position, performed the next day.

The programmer uses a Merlin Patient Care System Programmer (model 3650; St. Jude Medical, St. Paul, MN) with a universal serial bus interface to a Nanostim external module (Nanostim link). The module uploads Nanostim software to the Merlin programmer and provides an interface between the programmer and standard ECG electrodes placed on the subject's torso for 2-way communication with the implanted pacemaker and display of the surface ECG. The programmer displays the patient's ECG and the status of the implanted LCP, and it sends commands to change LCP parameter settings as directed by a user. The programmer transmits signals to an implanted LCP via conducted communication with subliminal 250-kHz pulses applied to the skin electrodes. Data are encoded in high-frequency pulses between surface electrode and pacemaker tip/ring during the refractory period that do not elicit a physiological response (and are not felt by the patient). It automatically selects an optimal skin-electrode pair for reception from an LCP. Apart from this conducted communication, it has the same operating principle as a conventional pacemaker programmer. The nominal pacing amplitude and sensing thresholds were 2.5 V and 2.0 mV, respectively. The estimated battery life of the LCP, based on accelerated lithium-cell test data in VVIR mode (pulse amplitude 2.5 V, pulse duration 0.4 ms, rate 60 bpm, and impedance 500 ohms) is 8.4 years with 100% pacing and 12.4 years with 50% pacing. The LCP is an RV blood temperature–responsive, rate-adaptive pacemaker, and can increase the pacing rate in response to exercise.[10,11]

Statistical Analysis

Continuous variables are expressed as mean value±standard deviation. We used a paired *t* test to compare performance values between implant (baseline) and 90 days. $P<0.05$ was considered indicative of statistical significance. Statistical calculations were performed by using SPSS 12.0 (SPSS Inc, Chicago, IL). The procedure duration was defined as the time from the insertion of the introducer sheath to removal. The time to hospital discharge was defined as the time from sheath removal to discharge from the hospital.

Results

Baseline Demographics and Implantation Details

The clinical characteristics of the patients are shown in the Table. The mean age of the cohort was 77±8 years (range, 53–91), and 67% of the patients were male (n= 22/33). The most common
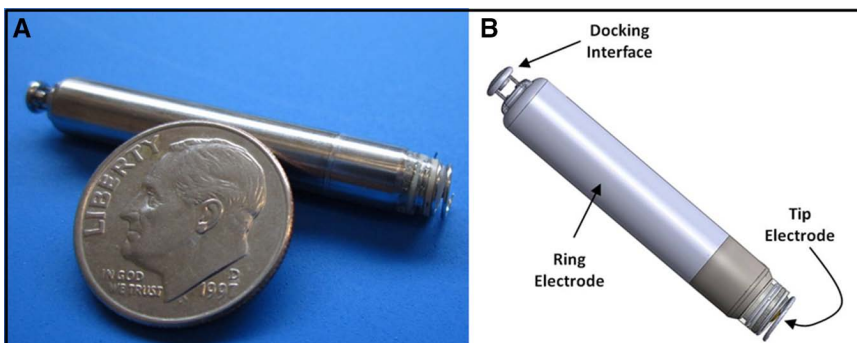

Figure 1. Leadless cardiac pacemaker. **A,** Picture of the leadless cardiac pacemaker with a US dime to indicate scale. **B,** Rendering of the device with pertinent components labeled.
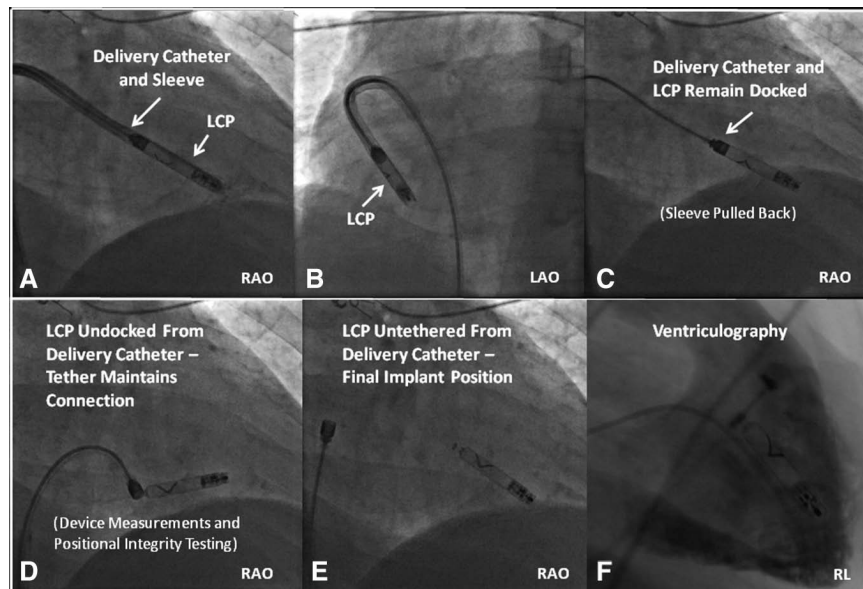
Figure 2. Fluoroscopic views of the LCP implantation procedure. **A** and **B**, The delivery catheter and LCP positioning in the RV apex in RAO and LAO views, respectively. **C**, The withdrawal of the delivery sleeve and maintenance of the connection between the LCP and the delivery catheter. **D**, Demonstration of positional integrity testing with downward and upward traction applied to the LCP, while the device remains tethered to the delivery catheter. **E**, Final implant position of the LCP once the delivery catheter has been undocked from the LCP. **F**, Ventriculogram of the final implant position at the RV apex. LAO indicates left anterior oblique; LCP, leadless cardiac pacemaker; RAO, right anterior oblique; RL, right lateral; and RV, right ventricular.

indication for cardiac pacing was permanent AF with AV block (n=22, 67%), followed by normal sinus rhythm with second or third degree AV block and with a low level of physical activity or short expected lifespan (n=6, 18%), followed by sinus bradycardia with infrequent pauses or unexplained syncope with electrophysiological findings (n=5, 15%). The implant success rate was 97% (n=32), and the majority of patients (n=23, 70%) did not require any repositioning of the LCP after its initial deployment. Five patients (15%) required the use of >1 LCP during the procedure owing to either the inadvertent placement of the device in the left ventricle (n=1), a malfunction of the release knob (n=1), delivery catheter damage related to tortuosity of the venous vasculature (n=1), damage to the LCP helix during insertion (n=1), or difficulty with the wire deflection mechanism of the delivery catheter (n=1). The mean procedure duration was 28±17 minutes (range, 11–74 minutes) and the average time to hospital discharge was 31±20 hours (range, 17–113 hours).

Performance Measures

The performance measures, including mean R-wave amplitude, pacing threshold (measured at 0.4 ms pulse width),
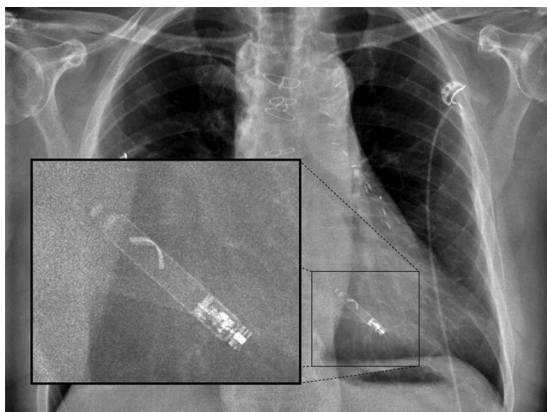

Figure 3. Chest x-ray after LCP implant. X-ray (posterior-anterior view) of the LCP position, which was performed the day after implantation. LCP indicates leadless cardiac pacemaker.

and impedance at implantation, predischarge, and 2-, 6-, and 12-week follow-up is shown in Figure 4. In comparison with implantation, there was a significant improvement at 12 weeks in the mean R-wave amplitude (+2.3 mV, $P<0.0001$), mean pacing thresholds (−0.31 V, $P=0.0011$), and mean impedance (−143.8 ohms, $P=0.0002$). The burden of pacing was 37±29% (range, 3%–99%), 39±26% (range, 5%–96%), and 42±31% (range, 1%–100%) at 2 weeks, 6 weeks, and 12 weeks, respectively.

Magnet mode (VOO pacing at 90 bpm) was operational in all patients tested before discharge (100%, n=31/31); 1 patient was inadvertently not checked before discharge, but the magnet mode was functional at the 12-week assessment, and 1

Table.   Baseline Demographics, Indications for Pacing, and Procedural Details

Parameter	(n=33)
Age, y	76.5±8.4
Male, n (%)	22 (67)
Pacing indication, n (%)	
Permanent AF with AV block (including AF with a slow ventricular response)	22 (67)
Sinus rhythm with 2nd/ 3rd degree AV block and significant comorbidities	6 (18)
Sinus bradycardia with infrequent pauses or unexplained syncope	5 (15)
Implant success rate, n (%)	32 (97)
Procedure duration, min	28±17
Time to hospital discharge, h	31±20
Repositioning attempts (to achieve final implant position), n (%)	
0	23 (70)
1	4 (12)
2	4 (12)
3	2 (6)
Rehospitalized within 90 days, n (%)	3 (9)
Complication-free rate, %	94

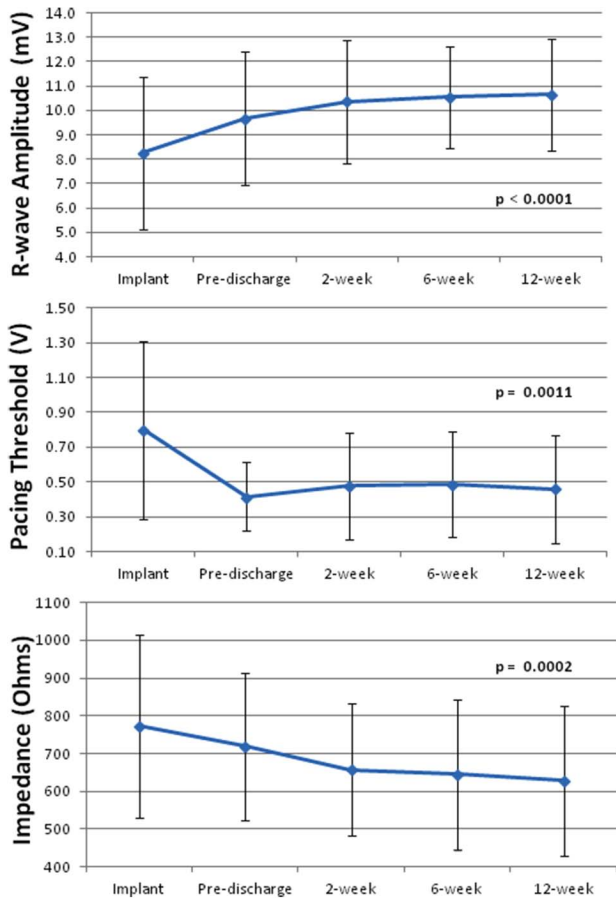AF indicates atrial fibrillation; and AV, atrioventricular block.

Figure 4. Device performance measurements of the leadless cardiac pacemaker. **Top, Middle,** and **Bottom** represent the mean value±standard deviation of the R-wave amplitude, pacing threshold (at 0.4 ms), and pacing impedance (ohms), respectively, at each follow-up assessment. *P* values shown represent the difference between the respective values at implant and at 12 weeks of follow-up.

patient died during the index hospitalization (see below). The majority of patients (n=29/31) performed the 6-minute walk test at both the 2-week and 6-week visits; the remaining 2 patients were in wheelchairs and did not perform the 6-minute walk test. At 12 weeks, 12 of 32 patients (38%) were reprogrammed from VVI to VVIR mode.

Safety

The overall complication-free rate was 94% (31/33). There was 1 serious adverse device effect. A 70-year-old man with persistent slow AF and previous embolic infarct of the kidney developed cardiac tamponade with hemodynamic collapse after repositioning of the LCP and manipulation of the delivery catheter in the RV apex, but before final release of the LCP. The patient underwent immediate reversal of anticoagulation, percutaneous pericardial drainage, and emergent median sternotomy on cardiopulmonary bypass with surgical repair of a perforation of the RV apex. After 24 hours of therapeutic hypothermia, the patient was extubated and recovering. However, on postprocedural day 5, he developed acute-onset left-sided hemiplegia attributable to a right-sided main cerebral artery ischemic infarct (international normalized ratio=1.5 on the day of the infarct and prophylactic dose

of low-molecular-weight heparin) and progressive cerebral edema. The patient died on postprocedure day 18.

In 1 patient, the LCP was implanted in the apex of the heart with acceptable device performance measurements. But soon after device release, it was recognized by multiple plane fluoroscopy and contrast ventriculography that the device was in the left ventricle (LV). The patient had a patent foramen ovale, through which the deflectable delivery sheath had inadvertently transited, thereby permitting access to the LV. After giving a 7000 IU heparin bolus, a trilooped snare retrieval catheter was advanced through the patent foramen ovale, the LCP was engaged and removed, and a new device was implanted in the RV apex. Retrieval of the device from the LV took 6 minutes. Although the patient did not experience any permanent clinical sequelae, it is possible that, had the event not been recognized, it could have led to an adverse outcome.[12]

One patient, 86 years of age with preserved LV function, who had the LCP implanted for recurrent syncope in the setting of sinus rhythm with second degree AV block and limited mobility, was readmitted 2 days later for recurrent syncope. A repeat chest x-ray confirmed stable positioning of the LCP in the RV apex, and the performance measures were stable and unchanged. Inpatient cardiac monitoring revealed monomorphic ventricular tachycardia (VT) at 260 bpm, accompanied by syncope. The LCP was removed (by the use of the single-looped snare retrieval catheter) on postimplant day 5, and a subsequent workup revealed nonobstructive coronary artery disease and a focal area of scar (delayed enhancement) in the basal posterior wall of the LV by cardiac MRI. He subsequently underwent implantation of a single-chamber transvenous implantable cardioverter-defibrillator (ICD) system, and was initiated on β-blocker therapy. He was readmitted ≈2 weeks later for appropriate ICD shocks attributable to VT at 260 bpm.

Three patients (9%) were rehospitalized within 90 days, 1 patient for an elevated international normalized ratio (international normalized ratio=9.3, without bleeding), 1 patient for an acute exacerbation of chronic obstructive lung disease, and 1 patient for the aforementioned VT. There were no instances of vascular injury (deep vein thrombosis, femoral hematoma, fistula, or pseudoaneurysm) requiring intervention for treatment, causing long-term disability or resulting in a prolonged hospitalization.[13]

Discussion

This is the first study of a permanent, completely self-contained, leadless cardiac pacemaker in humans. We have demonstrated that leadless pacing is feasible and safe in a consecutive series of patients with an indication for single-chamber ventricular pacing. The LCP was successfully implanted in 97% of patients, and the observed complication-free rate was 94%. This rate compares favorably with conventional pacing systems. After 3 months of follow-up, the measures of pacing performance were all improved.[14] No patient required a revision of the system (following the index procedure), and all implants demonstrated an adequate safety margin in comparison with the LCPs nominal pacing amplitude (2.5 V) and sensing threshold (2.0 mV).

The transvenous lead is a critical component of conventional cardiac pacemakers, but it is also their Achilles heel.[15] Despite improvements in lead design, lead malfunction is associated with significant adverse clinical outcomes and remains the most common reason for surgical pacemaker revision.[3,16] In a large registry comprising >28 000 patients, lead complications requiring reoperation (3.6%) were the most common complication within 3 months of pacemaker implantation.[17] A pacing system that eliminates leads as conduits for energy transfer could prove advantageous by minimizing the risk for lead-related infections, venous obstruction, and tricuspid valve damage/insufficiency.[18] Indeed, avoidance of intravascular leads has already been incorporated into ICD systems with the introduction of the fully subcutaneous ICD.[19] Furthermore, the LCP, and the lack of a subcutaneous pulse generator, would obviate the short-term mandated restriction of arm movement and weight bearing of conventional pacing systems. The absence of a separate pulse generator also mitigates the risk of either pocket erosion or pocket hematoma, the latter which can be associated with infection, prolonged hospitalization, and reoperation.[20] Finally, the LCP eliminates the possibility of intrasystem connector issues, such as loose set screws and air in the header, because the endocardial pacing electrode and pulse generator are a single unit.

There are other leadless cardiac pacing systems in development, they require 2 components – a subcutaneous energy transmitter (pulse generator) and a receiver electrode in the cardiac chamber.[21–23] These systems use energy delivery sources (ultrasound waves and alternating magnetic fields) whose safety and efficiency are still under investigation, and the potential for interference from external sources needs further investigation.[24] On the other hand, the LCP system delivers stimulatory impulses in a manner similar to conventional cardiac pacemakers and is not subject to environmental interferences inherent in multicomponent systems.

Although safe overall, there was 1 patient in this series who experienced cardiac tamponade during LCP implantation. The most likely cause for RV perforation was incomplete detachment of the LCP during repositioning with subsequent advancement of the protective sleeve beyond the tip of the LCP. The protective sleeve is intended to shield the helix from damage during insertion of the LCP into the venous system, and was designed to be retracted before contact with the myocardium. Preclinical bench testing for tip pressure demonstrated that, with the protective sleeve retracted, the pacemaker applies 4.6 g/mm^2; which is comparable to the tip pressure (5.5 g/mm^2) applied by a standard defibrillator lead (Medtronic 6936) with the stylet retracted. However, the force exerted on the myocardium with the sleeve extended beyond the tip of the LCP is 3.8 times greater (17.7 versus 4.6 g/mm^2).

As mentioned previously, in 1 patient the LCP was inadvertently implanted into the LV, but successfully retrieved despite having already been screwed into the myocardium and disengaged from the delivery catheter. Although unintentional, this event did demonstrate 2 important aspects of this system. First, although the LCP had undergone extensive preclinical testing to demonstrate device retrieval after untethering from the delivery catheter, this is the first clinical demonstration of this capability. This was further demonstrated in the other patient who required ICD implantation 5 days after LCP implantation because of symptomatic VT. Given that the device was able to appropriately pace and sense the LV, albeit for a short time, it raises the possibility that once multiple LCPs are able to cocommunicate, there is potential for multisite leadless pacing (right atrium/ventricle and biventricular).

Limitations

The LCP is only a VVIR pacemaker and is not appropriate for patients requiring dual-chamber sensing and pacing. Nevertheless, in the United States and Europe, nearly 20% and 30% of newly implanted pacemakers, respectively, are VVIR systems, and in developing countries, this number is even higher, often exceeding the number of dual-chamber pacemakers.[1] Furthermore, it is anticipated that leadless dual-chamber (multisite) pacing will become possible with further development. Only a randomized trial with a control group could prove the hypothesis that there would be more complications with traditional pacemakers. Furthermore, there is the possibility of complications with a leadless pacing system not seen with conventional pacing systems. For example, although not seen in this series of patients, we cannot exclude the possibility of device dislodgment and migration into the pulmonary vasculature. The LCP has a wider diameter than conventional pacing leads, which raises the possibility of mechanically induced proarrhythmia. Although 1 patient did present with sustained VT, the arrhythmia recurred weeks after the LCP was removed and further assessment revealed a previously undiagnosed area of scar in the LV. The LCP system requires an 18F venous introducer sheath, and although there were no vascular complications in this series of patients, their safety profile within the context of cardiac pacemaker implantation still requires further study. Torturous venous systems and anatomic variations may introduce additional challenges to implantation. Larger studies and serial follow-up will be necessary to assess this and other potential complications. Patients were followed for 90 days postimplant (the maturation time of the interface between an electrode and myocardium), which is the follow-up duration of comparable devices in studies for regulatory approval. Nevertheless, it is possible that an extended duration of follow-up might identify previously unseen functional or mechanical issues. Although, in this series of patients, we were able to safely remove 1 device acutely (from the LV) and 1 subacutely (from the RV, at 5 days), the safety and efficacy of retrieving the device (acute or chronic), especially with regard to the potential complications associated with manipulation of large retrieval catheters/sheaths within the RV, requires confirmation. Future studies will need to address the safety/efficacy of alternate-site RV pacing (ie, base, septum, and outflow tract), especially with regard to minimizing the potential deleterious effects of chronic RV apical pacing.

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CLINICAL PERSPECTIVE

Although highly effective, conventional cardiac pacemakers are limited by potential short- and long-term complications related to either the transvenous leads or the subcutaneous pulse generator. Thus, there has been intense interest in developing leadless cardiac pacemakers. Although it has been >40 years since the first preclinical demonstration of a leadless pacemaker, this study represents the first example of completely self-contained leadless cardiac pacing in humans. Thirty-three patients, with a clinical indication for single-chamber pacing, underwent implantation of a novel leadless cardiac pacemaker (LCP) able to function in a VVIR mode. After femoral venous access, the LCP is advanced to the right ventricle by using an 18F delivery system, and is then affixed to the myocardial tissue with the screw-in helix. We report that the procedure is feasible (implant success rate of 97%) with a mean procedure duration of 28±17 minutes and a favorable safety profile (complication-free rate of 94%). After 3 months of follow-up, all measures of pacing performance (lead impedance, pacing, and sensing threshold) either improved or were stable within the acceptable range. By eliminating the need for the weakest link of conventional pacing systems (the lead), and the need for a subcutaneous pulse generator, as well, this report represents a paradigm shift in cardiac pacing.