Permanent Leadless Cardiac Pacing: Results of the LEADLESS Trial

Running title: Reddy et al.; Leadless Cardiac Pacemaker

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Abstract

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 (LCP).

Methods and Results—The primary safety endpoint was freedom from complications at 90 days. Secondary performance endpoints 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 LCP during the procedure. One patient developed right ventricular perforation and cardiac tamponade during the implant procedure, and eventually died as a result of 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 stably within the accepted range.

Conclusions—In a prospective non-randomized 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 Information—Clinicaltrials.gov. Identifier: NCT01700244.

Key words: leadless cardiac pacemaker, pacemaker
Introduction

Nearly 250,000 new cardiac pacemakers are implanted annually in the United States, and an additional 750,000 are implanted worldwide.\(^1\) While 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 due 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 co-morbidities which 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 more than 40 years since the conception of a totally self-contained cardiac pacemaker, till 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 thirty-three patients.

Methods

Study Design

LEADLESS is a prospective, non-randomized, 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 i) permanent atrial fibrillation (AF) with atrio-ventricular (AV)
block (which includes AF with a slow ventricular response), ii) normal sinus rhythm with 2\textsuperscript{nd} or
3\textsuperscript{rd} degree AV block with a low level of physical activity or short expected lifespan, or iii) sinus
bradycardia with infrequent pauses or unexplained syncope with electrophysiology findings (eg,
prolonged HV interval).\(^8\) Patients were excluded if pacemaker-dependent, had a mechanical
tricuspid valve prosthesis, pulmonary hypertension, pre-existing pacemaker/defibrillator leads, or
an inferior vena cava filter. Follow-up assessments were performed pre-discharge and 2, 6, and
12-weeks post-implantation. At the 2-week follow-up visit, capable patients underwent a six-
minute walk test (6MWT), with the device programmed to VVIR (rate-responsive) calibration
mode.\(^9\) The implanting physician was provided the results of this examination, and
programming of the device (i.e. rate-response on or off) was left to their discretion. Patients
were enrolled after written informed consent. The patients were implanted between December
2012 and April 2013 in the three participating centers. The local institutional review board for
each participating center approved the study (clinicaltrials.gov no. NCT01700244).

**Safety Endpoints**

The primary safety endpoint was freedom from complications (complication-free rate), defined
as serious adverse device effects (SADE) at 90-days. Safety was measured by reporting the
complication-free rate (CFR), based on subjects who complete their 90-day follow-up visit or
drop out due to a complication. The secondary safety endpoint was implant success rate (ISR),
declared as the percentage of subjects leaving the implant procedure with an implanted and
functioning LCP device. The secondary performance endpoints 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 (pre-discharge) and six-minute walk tests (at the 2-week visit if 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 intra-cardiac device which 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 non-retractable, 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 inter-electrode distance is >10 mm. The pacemaker’s proximal end has a feature for docking the delivery and retrieval catheters.

After placing a 30 cm 18Fr sheath in the femoral vein (most commonly the right femoral vein), the device is delivered to the right ventricle (RV) using 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 maintaining a tethered connection 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 re-engaged, unscrewed and repositioned. The system also includes single or triple loop snare retrieval catheters which 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, Minnesota) with a universal serial bus (USB) 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 two-way communication with the implanted pacemaker and display of the surface ECG. The programmer displays the patient’s electrocardiogram 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 is encoded in high-frequency pulses between surface electrode and pacemaker tip/ring during the refractory period that do not elicit a physiologic 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 ± SD. 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 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 Table 1. The mean age of the cohort was 77 ± 8 years (range, 53 to 91) and 67% of the patients were male (n = 22/33). The most common indication for cardiac pacing was permanent AF with AV block (n = 22, 67%), followed by normal sinus rhythm with 2nd or 3rd 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 EP 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 due to either 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) and difficulty with the wire deflection mechanism of the delivery catheter (n = 1). The mean procedure duration was 28 ± 17 minutes (range, 11 to 74 minutes) and the average time to hospital discharge was 31 ± 20 hours (range, 17 to 113 hours).

Performance Measures

The performance measures, including mean R-wave amplitude, pacing threshold (measured at 0.4 ms pulse width) and impedance at implant, pre-discharge, 2, 6 and 12 week follow-up is
shown in Figure 4. As compared to implant, 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 prior to discharge (100%, n = 31/31); one patient was inadvertently not checked prior to discharge but the magnet mode was functional at the 12-week assessment, and one 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 two patients were in wheelchairs and did not perform the 6MWT. At 12-weeks, 12 of 32 patients (38%) were re-programmed from VVI to VVIR mode.

Safety
The overall complication-free rate was 94% (31/33). There was one serious adverse device effect. A 70 year old man with persistent slow AF and prior 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 prior to final release of the LCP. The patient underwent immediate reversal of anti-coagulation, 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 post-procedural day five, he developed acute-onset left-sided hemiplegia due to a right-sided main cerebral artery ischemic infarct (INR = 1.5 on the day of the infarct and prophylactic dose of low molecular weight heparin) and progressive cerebral edema.
The patient expired on post-procedure day eighteen.

In one 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 (PFO), through which the deflectable delivery sheath had inadvertently transited; thereby permitting access to the left ventricle. After giving a 7000 IU heparin bolus, a tri-looped snare retrieval catheter was advanced through the PFO, the LCP was engaged and removed, and a new device was implanted in the RV apex. Retrieval of the device from the LV took six 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.\textsuperscript{12}

One patient, 86 years old with preserved left ventricular function, who had the LCP implanted for recurrent syncope in the setting of sinus rhythm with 2\textsuperscript{nd} degree AV block and limited mobility, was re-admitted 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. In-patient cardiac monitoring revealed monomorphic ventricular tachycardia (VT) at 260 beats per minute, accompanied by syncope. The LCP was removed (using the single looped snare retrieval catheter) on post-implant day 5 and a subsequent work-up revealed non-obstructive 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 ICD system, and was initiated on beta-blocker therapy. He was re-admitted approximately 2 weeks later for appropriate ICD shocks due to VT at 260 bpm.

Three patients (9\%) were re-hospitalized within 90 days, one patient for an elevated INR
(INR = 9.3, without bleeding), one for an acute exacerbation of chronic obstructive lung disease and one 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 compares favorably to 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 compared to 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 is also its 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 more than 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 implantable cardioverter-defibrillator...
(ICD) systems with the introduction of the fully subcutaneous ICD (S-ICD). 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 re-operation. Finally, the LCP eliminates the possibility of intra-system connector issues, such as loose set screws and air in the header, since the endocardial pacing electrode and pulse generator are a single unit.

There are other leadless cardiac pacing systems in development, they require two components – a subcutaneous energy transmitter (pulse generator) and a receiver electrode in the cardiac chamber. These systems utilize 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. 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 to multi-component systems.

While overall safe, there was one patient in this series that 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 prior to contact with the myocardium. Pre-clinical bench testing for tip pressure demonstrated that with the protective sleeve retracted, the pacemaker applies 4.6 g/mm²; which is comparable
to the tip pressure (5.5 g/mm²) 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 vs. 4.6 g/mm²).

As mentioned previously, in one patient the LCP was inadvertently implanted into the left ventricle, but successfully retrieved despite having already been screwed into the myocardium and disengaged from the delivery catheter. Although unintentional, this event did demonstrate two important aspects of this system. First, while the LCP had undergone extensive pre-clinical 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 left ventricle, albeit for a short time, it raises the possibility that once multiple LCPs are able to co-communicate, there is potential for multi-site leadless pacing (right atrium/ventricle and bi-ventricular).

**Limitations**

The LCP is only a VVIR pacemaker and is not appropriate for patients requiring dual-chamber sensing and pacing. Nevertheless, in the US 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. Furthermore, it is anticipated that leadless dual-chamber (multi-site) 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 pro-arrhythmia. Although one 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 left ventricle. The LCP system requires an 18Fr 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 post-implant (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 one device acutely (from the LV) and one sub-acutely (from the RV, at 5 days), the safety and efficacy of retrieving the device (acute or chronic), especially with regards 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 (i.e. base, septum, and outflow tract); especially with regards to minimizing the potential deleterious effects of chronic RV apical pacing.

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**Conflicts of Interest Disclosures:** Dr. Reddy, Dr. Knops and Dr. Kautzner have received grant support from Nanostim Inc. Dr. Reddy has received stock options in Nanostim. BS Jacobson and A. Ostroff are employees of Nanostim. The remaining authors have no potential conflicts of
interest. A portion of this study was presented as a Late Breaking Clinical Trial at the Heart Rhythm Society Annual Scientific Sessions Denver, CO 2013.

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Table 1. Baseline Demographics, Indications for Pacing and Procedural Details

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<tr>
<td>Age (years)</td>
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<td>Male</td>
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<tr>
<td><strong>Pacing Indication</strong></td>
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<tr>
<td>permanent AF with AV block</td>
<td>22 (67%)</td>
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<tr>
<td>sinus rhythm with 2nd/3rd degree AV block and significant co-morbidities</td>
<td>6 (18%)</td>
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<tr>
<td>sinus bradycardia with infrequent pauses or unexplained syncope</td>
<td>5 (15%)</td>
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<tr>
<td><strong>Implant Success Rate (ISR)</strong></td>
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<tr>
<td>Procedure Duration (min)</td>
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<tr>
<td>Time to Hospital Discharge (hours)</td>
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<tr>
<td>2</td>
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<tr>
<td>3</td>
<td>2 (6%)</td>
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<tr>
<td><strong>Rehospitalized within 90 days</strong></td>
<td>3 (9%)</td>
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<tr>
<td><strong>Complication-free rate</strong></td>
<td>94%</td>
</tr>
</tbody>
</table>

**Figure Legends:**

**Figure 1.** Leadless Cardiac Pacemaker. Panel A is a picture of the leadless cardiac pacemaker with a US dime to indicate scale. Panel B is a rendering of the device with pertinent components labeled.

**Figure 2.** Fluoroscopic views of the leadless cardiac pacemaker (LCP) implantation procedure. Panels A and B shows the delivery catheter and LCP positioning in the RV apex in RAO and LAO views, respectively. Panel C shows the withdrawal of the delivery sleeve and maintenance
of the connection between the LCP and the delivery catheter. Panel D demonstrates positional integrity testing with downward and upward traction applied to the LCP, while the device remains tethered to the delivery catheter. Panel E represents the final implant position of the LCP once the delivery catheter has been undocked from the LCP. Panel F is a ventriculogram of the final implant position at the RV apex.

**Figure 3.** Chest X-ray after LCP Implant. X-ray (posterior-anterior view) of the LCP position, which was performed the day after implantation.

**Figure 4.** Device performance measurements of the leadless cardiac pacemaker. Top, Middle and Bottom panels represent mean value ± SD 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.
Figure 4
Permanent Leadless Cardiac Pacing: Results of the LEADLESS Trial

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