INNOVATIVE TECHNIQUES

Advances in Pacing Therapy: Examining the Potential Impact of Leadless Pacing Therapy

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ABSTRACT. In over 50 years of development, the permanent pacemaker has undergone remarkable advances. Nothing is more evident than the reduction in weight from over 300 g to less than 30 g. The leadless percutaneously implanted permanent pacemaker is presently approved in Europe and under clinical study in the United States. It provides another order of magnitude reduction to approximately 2 g and less than 1 mL. The leadless pacemaker appears to also offer opportunities to resolve many of the remaining concerns about pacemakers with implanted leads. This includes avoidance of lead-related complications, from fracture to extraction challenges, avoidance of pocket-related complications such as infection and disfigurement, and magnetic resonance imaging incompatibility. However, there remain limitations, including a need for learning new insertion techniques, substantial reimbursement hurdles, and limited indications due to the single chamber right ventricular pacing mode capability. Clinical trial experience may further elucidate additional limitations and advantages. Future possibilities for further improvement in the leadless pacemaker are discussed, including the potential for dual-chamber sensing, dual-chamber pacing, biventricular pacing, and defibrillation capability, in association with a subcutaneous implantable cardioverter-defibrillator.

KEYWORDS. artificial, cardiac, cardiac pacemaker, leadless pacing, pacing.

Introduction

First implanted in humans in 1958, transvenous permanent pacemakers have undergone incredible developmental advances in the past half century (Figure 1). From an initial size of over 300 g, current generators are under 30 g. However, many of the drawbacks noted with early pacemakers are present to this day:

- generator is remote from the heart
- requires intravascular leads
- frequent pocket-related concerns: discomfort, infection, hematoma
- frequent lead-related concerns: mechanical failures from movement, subclavian crush, lead-on-lead injury, challenges with removal
- patient-perceived limitations: cosmetic concerns, disfigurement, mobility restrictions, magnetic resonance imaging (MRI) compatibility, travel restrictions, postoperative wound care, self-perception concerns, size, product recalls
- physician concerns: radiation exposure, follow-up demands, technical challenges, reimbursement challenges, MRI compatibility.

The concept of a leadless pacemaker was developed decades ago. Interestingly, the relatively newer field, implantable cardioverter-defibrillators (ICDs), led this approach for leadless cardiac implantable electrical devices (CIEDs). Before the first ICD was implanted via thoracotomy, Michel Morowski envisioned an extracardiac lead system utilizing a superior vena cava (SVC) coil with an epicardial patch as an attempt to avoid intracardiac leads. Today, a truly extracardiac implantable defibrillator is available, the Boston Scientific S-ICD...
Figure 1: Photo of a patient in 1952 with the PM-65 pacemaker designed by Paul Zoll with leadless electrodes placed on the right and left sides of the chest wall.\textsuperscript{1}
(St. Paul, MN) though it still requires a large pulse generator and extrathoracic lead system placed in the subcutaneous tissue of the chest wall, designed to avoid intravascular complications.3

Beginning in 2014, there are two leadless pacemakers undergoing clinical study in the United States, the Nanostim (St. Jude Medical, St. Paul, MN) and the Micra transcatheter pacing system (Medtronic, Minneapolis, MN). As a result of recent technologic advances, these devices can potentially overcome many of the current pacemaker with lead concerns noted above.

Technological advances

Until recently, the potential for a true intracardiac pacemaker had been limited by two factors: 1) inability to communicate with a device remote from the chest wall using low current drain, and 2) shape restrictions with flat integrated circuit silicone chips. Both of these hurdles have been overcome. The St. Jude Medical Nanostim device utilizes conducted communication which reduces the peak current requirements seen with traditional inductive and radiofrequency (RF). The quiescent current is less than 0.7 mA, which is about one-tenth of that seen with a conventional pacing system. Programmed at 2.5 V, 0.4 ms, 60 ppm at 100% pacing the device is rated at 9.8 years longevity, which is comparable to a conventional VVIR pacemaker. At 25% pacing burden, the device has an expected longevity of 18.9 years, longer than that for conventional pacemakers. An adapter is available for the traditional programmer, which just requires surface electrodes for programming adjustments.

The Medtronic Micra device achieves communication using the standard Model 2090 Programmer, similar to standard Medtronic devices, using the Telemetry B communication protocol. Micra does not have a magnet mode with the pacing safety margin automatically confirmed on an hourly basis. Micra device longevity estimates are available via programmer but not publicized at present. By utilizing a single integrated circuit, the current drain with the Nanostim is approximately 10% of conventional pacemakers yet provides sensing, pacing, and communication capability.4 This low current communication scheme and electronics combined with a new high-density battery (lithium carbon monofluoride or CFX) allow for device miniaturization that enables percutaneous delivery of the totally self-contained device via the femoral vein. These shape changes have overcome the hurdle of the delivery system of the device being too large for percutaneous delivery.

The leadless pacemaker is a self-contained unit comprising a battery, low current electronics, and fixation mechanism in one form factor, thus obviating the need for any lead. As with traditional leads, these devices also utilize steroid elution to further reduce pacing thresholds. These new intracardiac pacemakers have further reduced the size of the implanted pacemaker by another factor of 10, now down to approximately 2 g and less than 1 mL, less than 1% the size of the original devices (Figures 2 and 3).

Leadless pacemaker implantation

These new miniaturized pacemakers are truly leadless (unlike the “leadless” S-ICD), delivered via the femoral vein percutaneously. These new advances provide several obvious benefits: there is no surgical pocket or lead, they are conditional MRI compatible, and there is no cosmetic disfigurement required with this surgery or mobility restriction.

While both of the devices are still under investigation in the United States, the novel approach presents some new implant challenges as cardiac electrophysiologists develop a new skill set to implant and undock these detachable devices. For example, retrieval for a generator change now requires a catheter-based snare system. Fortunately, the Nanostim trials have demonstrated a short learning curve, with times comparable to that of conventional pacemaker surgery.6 Although experienced pacemaker implanters uniformly raise concern about potential dislodgment of the leadless device, early experience suggests that the fixation system is quite stable. Once deployed, the acute pull-out force of the Nanostim device is over 300 g, substantially higher than the 60–100 g necessary for an acute active fixation pacing lead evaluated typically with a “tug test.”5,6 Of course, chronically implanted leads typically require over 1,000 g of force for extraction.7 The comparable data for the chronically implanted leadless pacemaker is not yet available.

As with any new procedure, there is a learning curve for implantation of the leadless pacemaker. Unlike an angiogram or electrophysiologic study where catheters are inserted and promptly removed, implantation of a pacemaker via the femoral vein requires strict surgical sterile precautions (careful prep, hat, mask, etc.). Preoperative prophylactic antibiotics should be administered as with any implanted device.

Once femoral venous access is achieved, the venotomy site must be upsized to accept the larger sheaths. In anticipation of later sheath removal, vein closure must be pre-planned. Three techniques have been utilized: 1) a figure-of-eight stitch after sheath removal for 4–24 h to assist with manual compression, 2) manual compression only with close observation, or 3) use of a closure device. For our Nanostim leadless cardiac pacemaker (LCP) insertions, we have adopted the last one, leveraging the experience of the interventional cardiologists with large arterial sheaths such as utilized in transluminal aortic valve replacement. After venous access, we commonly insert a 6F sheath and then two Preclose (Abbott Vascular, Redwood City, CA) sutures inserted at the 10:00 and 2:00 positions for later post-implant closure with the Perclose ProGlide SMC device, consistent with their instructions for use.5 This often allows for same-day discharge after leadless pacemaker surgery.

Once the 30-cm 18F (56 cm 23F for Medtronic) femoral venous sheath delivery system is inserted, the device is carefully opened and prepared for insertion. With the St. Jude Medical device, care must be taken to not damage the helical fixation coil as it can catch on surgical towels and other equipment, resulting in the admonition “protect the helix.” The Medtronic device uses a different fixation...
Figure 2: Design of the leadless pacemaker. (A) St. Jude Nanostim; (B and C) Medtronic Micra Images courtesy of St. Jude Medical and Medtronic Inc.
mechanism: four Nitinol (nickel titanium) tines which remain within the larger sheath until the device is deployed. The technique for sheath and pacemaker insertion requires training and practice. A right ventriculogram is beneficial to delineate the right ventricular apical/lower septal anatomy. The pacemaker is delivered across the tricuspid valve with use of a deflectable/steerable delivery catheter in both devices (Figure 4). The St. Jude device uses an extendable sleeve to protect the helix from intravascular damage (Figures 3 and 4). After the Nanostim protective sleeve is positioned in the right ventricle, care must be taken to avoid excessive

Figure 3: Depiction of a deployed leadless pacemaker in the right ventricular apex.

Figure 4: Leadless pacemaker delivery catheter and steerable sheath. Image courtesy of St. Jude Medical.
force against the endocardium, as perforation has been reported. A post-marketing study in Europe was temporarily halted following reports of perforations and deaths.9 After review, this experience suggested some revised implantation techniques to minimize the risk of implant-related cardiac tamponade. For example, excessive torque with the delivery sheath transmitted to the right ventricular apex may increase the risk for right ventricular apical perforation. Therefore, implanters are now instructed to pull back the protective sleeve/delivery sheath after it crosses the tricuspid valve without allowing the sheath to touch the right ventricular wall.

With the Micra device, the delivery catheter is advanced across the tricuspid valve in a similar fashion. Gentle pressure is maintained with the tip of the catheter in the desired location as the device is deployed. The Micra does not have a helix and thus doesn’t require torque force for deployment. The surface area of the delivery cup allows for secure device deployment directly to the myocardium. As the pacemaker exits the delivery catheter, the tines then fixate within the right ventricular endocardium.

Clinical trials

In the Nanostim Leadless Trial, the only manuscript published study to date with human data, investigators found a high implant success rate of 97% and short procedure duration (28 min, range 11–74 min “skin to skin”).10 The ongoing Leadless II FDA IDE trial will add to this experience with anticipation for completion of enrollment for up to 667 patients in late 2014 and study completion in 2015.11 The Micra Transcatheter Pacing Study began outside the United States (OUS) in December, 2013 and in the United States in February, 2014. The results from the first four OUS patients were recently reported without complications during 90 days of follow-up.12 As part of the company’s efforts to gain European CE mark approval for the device, approximately 60 patients will receive the Micra leadless pacemaker and will be followed for 3 months. For US approval, the Food and Drug Administration (FDA) mandated a minimum of 300 patients be followed for 6 months.13 Enrollment continues beyond that for up to 780 patients. ClinicalTrials.gov states that enrollment will complete in 2016 with study completion in 2018 for the Medtronic device.14 With both device trials, it is possible that interim data submission of trial results could expedite the approval process.

To date, studies have demonstrated that leadless intracardiac pacing is safe and feasible.15 However, longer-term study of safety and efficacy are needed. Early generations of the leadless pacemaker have less robust electrograms storage or programmable features than traditional pacemakers. However, they still provide the essential device data, pacing, and sensing programmability and a rate response feature. Rate response in the St Jude device is via a temperature sensor within the housing. The Medtronic device offers a three-axis accelerometer sensor to allow the physician to select an alternate axis to sense activity if the default axis provides suboptimal performance. In the Medtronic device rate response is provided by an accelerometer that rejects cardiac motion with a 1–10 Hz band pass filter. Battery longevity is estimated to be as much as 7–15 years due to the increased efficiency of the current source adjacent to the myocardium.

Retrievability

Traditional pacemakers pose challenges for removal. When intracardiac leads can be maintained, a generator change for end-of-service (EOS) management is often a relatively simple surgical procedure of reoperation at the chest wall device pocket. However, lead extraction carries a substantial risk and is necessary for a variety of reasons.15 For the leadless pacemaker, the two devices both utilize a catheter-based snare retrieval approach. However, the different leadless pacemakers take a different approach relative to EOS management. Initially, the Medtronic Micra will be labeled for retrieval acutely after implantation only. If replacement is needed subsequently, the recommendation is to deactivate the expired device and implant a new leadless pacemaker in the ventricle adjacent to it. Although experience is still ongoing, the St. Jude Medical Nanostim may be retrievable for a longer time interval post implantation. Published data show 100% successful retrieval in an in vivo ovine model 5 months post implantation with an average time for removal of just 155 seconds from retrieval catheter insertion to device removal.16 Results awaiting publication have documented successful retrieval in a chronic sheep model 2.5 years post implantation (n=8).17 Whether there is a clinical significant difference in retrievability of these two new leadless pacemakers has yet to be determined.

Current limitations

At present, leadless cardiac pacemakers offer only single right ventricular pacing, in modes VVI or VVIR. Currently in the United States over 82% of implanted pacemakers are dual chamber.18 Outside the United States, dual-chambered devices constitute 50–70% of device implants. A recent consensus statement recommended dual-chamber pacing in pacer-indicated patients with intact AV node conduction.19 Current leadless pacemaker study criteria limit indications to patients with one of these three criteria:

- permanent atrial fibrillation with bradycardia meeting standard pacemaker indications
- sinus rhythm with low level of physical activity or short expected lifespan (though over 1 year)
- sinus bradycardia with infrequent prolonged pauses, clinically or at electrophysiology study

Study exclusion criteria include patients with known pulmonary hypertension ≥40 mmHg or a pre-existing
transvenous pacemaker system, thus further limiting those who qualify.20

During the clinical trials, a major limitation to implantation has been the lack of adequate reimbursement. Currently in the United States, there are no approved ICD-9 billing codes that are specific for a leadless pacemaker. To achieve reimbursement, individual centers are required to negotiate with their local center for medical and medicare services (CMS) intermediary. Some intermediaries have linked the investigational leadless pacemakers to the standard single-chamber pacemaker with lead implantation code (CPT 33207) which has a relatively low reimbursement. Typical 2014 outpatient hospital reimbursement is $8790 plus $478 for physician services, including 90 days of post-implant care.11,22 Other carriers have even been unwilling to link reimbursement to that code requiring use of CPT 33999 outpatient procedure code, which limits hospital reimbursement to $500 or less. It is estimated that the miscellaneous cost of a leadless pacemaker implantation exceeds $4,000 in addition to the device itself. Furthermore, it is anticipated that the device vendors will charge a significant premium for these pacemaker systems once achieving FDA approval, likely in excess of $10,000. Thus, the true hospital cost for a leadless pacemaker, once FDA and CMS approved, may exceed $14,000. In the interim, hospital systems are forced to take a financial loss to participate in these clinical trials. At present, the enthusiasm of investigators has prompted prominent centers to enroll in these clinical trials, even with this financial loss. However, once approved, it is unlikely that this scenario will continue. Thus, the continued success of the leadless pacemaker may hinge on a non-clinical concern regarding adequate insurance reimbursement.

**Potential impact**

While the St. Jude Medical Nanostim leadless pacemaker has the CE mark and thus approval in Europe, it is still under FDA-monitored clinical investigation in the United States. The Medtronic Micra is under investigation in both the United States and Europe. Nevertheless, the clinical interest is great, as witnessed by the hospitals willing to subsidize the clinical trials just for the opportunity to implant these revolutionary devices. Despite the need for new implantation techniques the trials are proceeding well, so it is reasonable to presume that these devices will achieve FDA and CMS approval by 2016 in our estimation. The obvious advantages to the leadless form factor have resulted in characterization of leadless pacing as a disruptive technology likely to replace some of the $6 billion traditional pacemaker with lead market.23 The potential future impact of leadless pacemakers on the CIED market remains dependent on two factors: 1) reimbursement, and 2) future advances beyond single-chamber pacing. The research- and acquisition-related costs for the current leadless pacemakers by St. Jude Medical and Medtronic likely amount to over $250 million. In 2013, Nanostim alone was purchased by St. Jude Medical for $123.5 million upon reaching the milestone of CE mark approval with additional financial incentives for further milestone attainment.24 The Medtronic Micra was developed in-house but presumably has similar high developmental costs. In order for these expenses to be recouped, the vendors anticipate a new CMS Outpatient Prospective Payment System (OPPS) category with higher reimbursement than the current single-chamber pacemaker, as explained above. In the current fiscal environment, it is unlikely that either vendors or payors would be willing to lose money on leadless pacemaker implantations, even with pressure from consumers and physicians. The baseball prognosticator Yogi Berra famously stated, “It is difficult to make predictions, especially about the future.”25 Nevertheless, the continued advance of technology suggests that future advances in the leadless pacemaker field will be forthcoming. It is likely that a variation of dual-chamber pacing will be the next advance. It is reasonable to assume that a single-chamber device could be developed with remote atrial far-field sensing, useful for tracking atrial rates in an atrial-sensed, ventricular-paced VDD mode. Consistent with the recent guidelines, intact AV conduction could be maintained for indicated patients.8 Of course, VDD pacing would preclude ventricular synchronous dual-chamber pacing, DVI mode. Single-chamber pacing in the atrium alone, AAI mode, could potentially be possible with this current generation of leadless pacemakers. However, reports have found that 57–67% of patients with sick sinus syndrome have concomitant abnormal AV conduction, explaining why atrial single-chamber pacemakers are rarely used today.26,27 It is estimated that over 60% of current dual-chamber pacemaker implantations are for patients with intermittent AV conduction disease with or without sinus node dysfunction. This suggests that sensing and pacing of both the atrium and the ventricle, DDI mode, will be necessary for leadless pacemakers to capture the majority of the current pacemaker with lead market. Thus, a separate leadless atrial pacemaker able to synchronize pacing with a leadless ventricular pacemaker will be necessary to achieve the traditional multifunctional DDD mode pacing. Any leadless dual-chamber system will need to be able to communicate beat-to-beat between the atrium and ventricle ideally with a programmable AV delay. In addition, a leadless dual-chamber pacemaker system will need to utilize minimal power to maintain acceptable longevity.

Current leadless pacemaker indications are restricted to patients who do not anticipate predominant ventricular pacing, unless the patient has a limited lifespan. Research, mostly in the past decade, has documented that predominant right ventricular pacing causes dysynchronous left ventricular activation and contraction often progressing to compromised left ventricular function and clinical heart failure.28,29 Regardless of whether a pacemaker has a lead or not, biventricular pacing has become the standard for patients anticipated to require predominant ventricular pacing. The well-received BLOCK-HF trial found that patients with AV block and an ejection fraction of 50% or less had a 26% lesser chance of developing heart failure or
its surrogate if biventricular pacing was instituted at initial implant. Thus, a leadless biventricular pacemaker will eventually be necessary before leadless pacing replaces all transvenous pacemakers with leads. The development of a leadless pacemaker solely for the left ventricle could reignite discussion about the necessity for biventricular versus left ventricular pacing alone.

In the near future, it is unlikely that implanted defibrillator technology will be replaced entirely with an intravascular leadless device. An intravascular, percutaneously placed ICD (Innerpulse, Synecor, Chapel Hill, NC) has been studied, but the project remains dormant due to regulatory, financial, and technological hurdles. Nevertheless, in selected patients, it may be possible to envision a subcutaneously implanted ICD coupled with a leadless ventricular pacemaker able to provide both bradycardia pacing support and antitachycardia pacing. One of the present limitations of the S-ICD is the inability to provide asymptomatic pacing therapy.

Finally, the potential for both leadless and ‘‘deviceless’’ pacemaker surgery is under study using gene therapy. A biological pacemaker has been successfully tested in a porcine model of heart block by delivering a gene encoding the T-box 18 transcription factor to the right (or potentially left) ventricular myocardium. Cardiomyocytes with sinus node-like activity were identified with heart rates and autonomic function within the physiologic range of 60–70 bpm. While this has yet to be tested in humans and is presently being considered only for temporary support after infected lead/device removal, the potential exists for another disruptive technology, true biological pacing.

Conclusion

In over 50 years of development, the permanent pacemaker has had remarkable advances. The leadless percutaneously implanted permanent pacemaker is likely to be another revolutionary advance. Approved in Europe but still under clinical study in the United States, the leadless pacemaker appears to offer opportunities to resolve many of the remaining concerns about pacemakers with implanted leads. This includes avoidance of lead-related complications, from fracture to extraction challenges, avoidance of pocket-related complications such as infection and disfigurement, as well as providing MRI compatibility and no postoperative mobility restrictions. However, there remain limitations, including a need for learning new catheter-based delivery system insertion techniques, substantial reimbursement hurdles, and limited indications due to the single-chamber right ventricular pacing mode capability. Future opportunities for improvement in the leadless pacemaker are discussed, including the potential for dual-chamber sensing, dual-chamber pacing, biventricular pacing, and defibrillation capability, in association with a subcutaneous ICD. The results of ongoing US trials regarding the safety and efficacy of leadless pacing are anxiously awaited.

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