Leadless Pacemakers

Mikhael F. El-Chami, MD*, Faisal M. Merchant, MD, and Angel R. Leon, MD

Leadless pacing is an emerging technology with the potential to significantly improve outcomes associated with the need for long-term pacing. Specifically, the major advantage of leadless systems is abolishing the need for transvenous leads and subcutaneous pockets, both of which account for most adverse events associated with traditional pacemakers. Two leadless pacemakers are currently available: the Nanostim (leadless cardiac pacemaker [LCP]) device (St. Jude Medical, Sylmar, California) and the Micra Transcatheter pacing system (Medtronic, Minneapolis, Minnesota). These 2 pacemakers have shown promising results in clinical trials. In conclusion, in this review we summarize the results of the 2 investigational device exemption trials and compare the pros and cons of these devices to traditional transvenous pacemakers. **(Am J Cardiol 2017;119:145−148)**

The introduction of "leadless" pacing systems as an alternative to traditional systems could potentially eliminate many of the described complications associated with transvenous leads and device pockets.[1,2] There are currently 2 available leadless pacing systems: the Nanostim (leadless cardiac pacemaker [LCP]) device (St. Jude Medical, Sylmar, California) and the Micra Transcatheter pacing system (TPS) (Medtronic, Minneapolis, Minnesota).

Leadless Pacing Systems

The 2 leadless pacing systems share some characteristics, including delivery through the femoral vein through a deflectable catheter, but they differ with respect to their dimensions, how they attach to the myocardium, and the type of rate response sensor used (Table 1).

The LCP is a 4.2 × 0.6-cm capsule-like device (Figure 1)[3] inserted into the right ventricle (RV) abutting the apical septum using an 18Fr deflectable sheath. The device attaches to the myocardium using an active fixation helix.[4] The TPS measures 2.6 × 0.7 cm (Figures 1 and 2), and requires a larger, 23Fr introducer. Unlike the LCP, it attaches to the myocardium through the use of nitinol tines. Both devices incorporate rate response features based on motion sensors. The LCP utilizes a temperature sensor, whereas the TPS uses an accelerometer technology to facilitate programmable rate response algorithms. Each device was designed to allow potential extraction/retrieval from the area of attachment.[3,4] However, in vivo data on the feasibility of extraction, particularly of chronically implanted leadless pacers, are limited. Two reports in abstract form are available. Animal data on chronic LCP implants retrieval were presented by Sperzel et al (2013)[5] and recently Reddy et al[6] presented the largest clinical experience with chronic device (LCP) retrieval (abstract presented at HRS 2016).

Clinical Data: Safety and Effectiveness

Nanostim LCP: The LEADLESS clinical evaluation of the Nanostim LCP enrolled 33 subjects with a need for ventricular pacing without an indication for atrial sensing or stimulation. Most patients in this study had atrial fibrillation and atrioventricular block.[7] Implanters successfully inserted the device in 97% (32 of 33) of subjects (the procedure was aborted in 1 patient after developing cardiac perforation during device repositioning). The 3-month complication-free rate was 94%, with 2 major adverse events. As mentioned earlier, 1 subject experienced an RV perforation, requiring urgent pericardiocentesis for pericardial tamponade followed by cardiac surgery to repair the perforation. The subject died 5 days later from a catastrophic stroke. A second subject underwent inadvertent insertion of the LCP into the left ventricle through a patent foramen ovale. This device was later retrieved and a new LCP was inserted into the RV. The reported 1-year follow-up of this trial noted no device-related complications from 3 to 12 months after implant.[8] Additionally, electrical parameters of the LCP were stable over 1-year follow-up.

The LEADLESS II clinical evaluation of the same pacing system prospectively enrolled 527 subjects in a non-randomized assessment of the performance of the LCP.[1] Implanters achieved success in 95.8% (504 of 527) of attempts. Major adverse events occurred in 6.5% of subjects, including cardiac perforation in 1.6%: hemopericardium not requiring intervention in 0.4%, hemopericardium requiring intervention in 0.2%, and pericardial tamponade requiring intervention in 1%. Acute device dislodgement occurred in 6 patients (1.5%): 4 of these devices migrated to the pulmonary artery and 2 to the femoral vein. In all cases, the dislodged devices were successfully retrieved percutaneously. An additional 0.8% of patients underwent device retrieval for elevated stimulation threshold during follow-up (mean time for retrieval 160 days). Vascular access complications occurred in 1.2% of subjects.

Department of Medicine, Division of Cardiology-Section of Electrophysiology, Emory University School of Medicine, Atlanta, Georgia. Manuscript received August 27, 2016; revised manuscript received and accepted October 4, 2016.

See page 148 for disclosure information.

*Corresponding author: Tel: 404-686-2504; fax: 404-686-4826.
E-mail address: melcham@emory.edu (M.F. El-Chami).

0002-9149/16/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2016.10.012

Table 1
Comparison of Nanosim leadless cardiac pacemaker (LCP) and Micra Transcatheter pacing system (TPS) features

	LCP	TPS
Length (mm)	41.4	25.9
Volume (cm3)	1	0.8
Weight (g)	2	2
Fixation mechanism	Screw-in helix	Nitinol tines
Pacing mode	VVI/R	VVI/R
Sensor	Temperature	Accelerometer
Battery Longevity (years)	9.8 (2.5 V @0.4 ms)* 14. 7 (1.5 V @ 0.24 ms)	4.7 (2.5 V @ 0.4 ms)* 10 (1.5 V @ 0.24 ms)

Adapted and modified from Sperzel et al[3] and Miller at.al.[4]
* Battery longevity based on ISO (International Organization for Standardization) for reporting battery longevity (2.5 V @ 0.4 ms), 600 Ohms and fixed pacing at 60 beats/min.

Figure 1. The Micra and Nanostim pacemakers.

Micra TPS: The Micra TPS investigational device exemption study, a multicenter prospective, nonrandomized clinical evaluation enrolled 725 subjects to evaluate the pacing system performance.[2] The evaluation compared outcomes in these subjects with a historical cohort of subjects enrolled in 6 prior Medtronic transvenous pacing system clinical evaluations.

Micra TPS implantation succeeded in 719 of 725 subjects (99.2%). The 6-month major complication rate was 4%, compared with a rate of 7.4% in the historical transvenous control group (hazard ratio 0.51, 95% confidence interval 0.33 to 0.75, $p = 0.001$). The Micra subjects were older and had more comorbidities compared with the historical cohort. The reduction in complication rates seen with the Micra cohort was even more pronounced when a matched group was used for comparison.

Complications included cardiac perforation in 1.6%, access-related issues in 0.7%, venous thromboembolism in 0.3%, and a rise in stimulation threshold despite the absence of overt dislodgement in 0.3%.

One subject died after implant from metabolic acidosis, underlying renal failure, and possibly sepsis. There was no evidence of mechanical complication related to the procedure. The rate of pericardial effusion in the Micra subjects was 1.6% compared with 1.1% in the historical cohort. This difference was not statistically significant. The absence of lead-related issues and device pocket infection could explain the lower rate of complications seen with the TPS compared with the transvenous pacing control. Electrical measurements at 6 months, including stimulation threshold, intracardiac signal amplitude, and pacing impedance remained excellent and stable in most patients (98.3%).

Comparing the LCP with TPS: The 2 currently commercially available leadless pacing systems eliminate the need for a subcutaneous pocket and the use of intravenous electrodes connecting the device to the myocardium, thus eliminating pocket- and lead-related complications. Table 2 summarizes the investigational device exemption trial results.[9]

The 6-month complication rate appears generally comparable between the 2 systems. Rates of pericardial effusion and groin complications are also similar. The rate of acute dislodgment appears higher with LCP; however, these 2 devices have not been compared head to head and any such comparisons should be considered hypothesis generating.

Comparing the leadless pacemakers to traditional pacemakers: The 4% to 6.5% complication rate observed in the early experience with leadless pacemakers compares favorably with the complication rate reported in clinical evaluations of transvenous pacing systems (Figure 3). Kirkfeldt et al[10] analyzed outcomes after cardiac device implantation and reported a 7.5% rate of complications in single-lead system implants and a 12.5% rate with dual-lead transvenous pacing systems. The FOLLOW PACE study reported a similar rate of complications (12.5%) after single- and dual-chamber pacemaker implantation.[11] Although leadless pacemakers compare favorably with transvenous pacemakers, it should be noted that the reported comparison in this manuscript (Figure 3) to dual- and single-chamber systems rather than single-chamber systems alone.

The rate of pericardial effusion reported during leadless system implants slightly exceeds that observed with traditional pacing system implants. The reported rate of pericardial effusion associated with transvenous pacing system implants approximates 1%, versus 1.5% and 1.6%, respectively, with LCP and TPS implants (Figure 4). A Mayo Clinic report documented a 1.2% incidence of pericardial effusion in over 4,000 transvenous system implants (including both single- and dual-chamber systems), similar to the 1.1% rate of pericardial effusion seen in the Micra historical cohort (average rate of the 6 studies included as a comparative cohort).[12] Pericardial effusion associated with leadless pacing system implants might require more aggressive intervention, including surgery, to correct myocardial perforation created by the larger-diameter delivery system and devices used in these implants.

Future implications: The early experience with the first-generation leadless pacing systems supports the potential for more widespread use of this novel technology. The decrease in pocket- and transvenous electrode-related adverse events provides leadless technology a promising advantage.

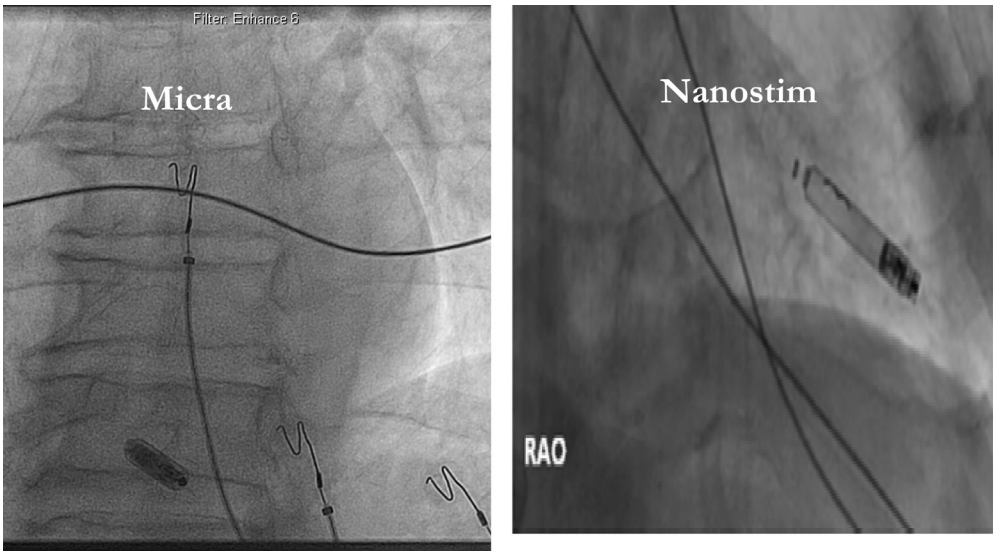

Figure 2. LAO fluoroscopy of a Micra pacemaker. RAO fluoroscopy of Nanostim pacemaker. LAO = left anterior oblique; RAO = right anterior oblique. Modified from Miller et al.

Table 2
Summary of Nanostim leadless cardiac pacemaker (LCP) and Micra Transcatheter pacing system (TPS) investigational device exemption (IDE) trials

Variables	Trials	
	Leadless II-LCP (n=526)	Micra-TPS (n=725)
Implant Success	95.8%	99.2%
Thresholds @ Implant (V@ms)	0.82 @ 0.4	0.63 @ 0.24
Threshold @ 6 Months (V@ms)	0.53 @ 0.4	0.54 V @ 0.24
Complication Rates (6 months)	6.5%	4%
Pericardial Effusion	1.5%	1.6%
Groin Complication	1.2%	0.7%
Device Dislodgement	1.1%	0%

Adapted and modified from Link.[9]

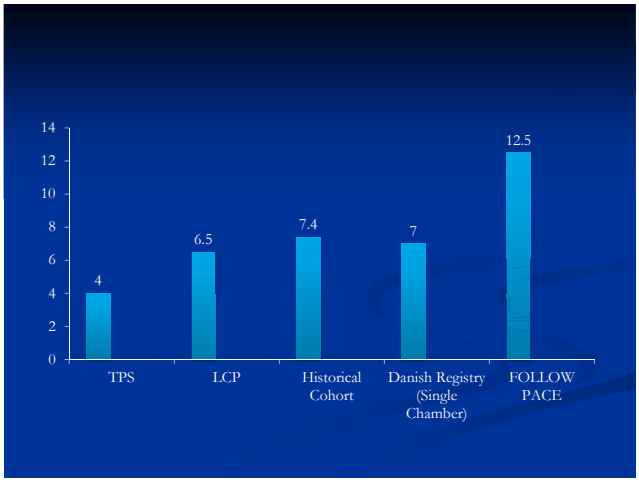

Figure 3. Complication rates of leadless and transvenous pacemakers.[1,2,10,11] Adapted and modified from Medtronic training (new implanters) slides.

Development of smaller and less traumatic delivery systems and devices will likely decrease associated complications. The evolution of technology will likely involve multichamber systems for dual-chamber stimulation and cardiac resynchronization.[3,4,13,14] Incorporation of leadless pacing technology into subcutaneous defibrillating systems (subcutaneous implantable cardioverter defibrillator [S-ICD]) to provide effective bradycardia rate support and antitachycardia pacing will greatly expand the applicability of these devices to a larger population.

Clearly, any evolving technology will need continuing clinical evaluation in larger populations to demonstrate the safety and efficacy of these newer generation systems.[15,16] Specifically, randomized controlled studies comparing leadless pacemakers with traditional transvenous systems will help identify the pros and cons of this technology.

Unanswered questions: The early results from clinical evaluations suggest that leadless pacing could gain wider adoption. Whether leadless systems expand beyond a small niche to replace traditional transvenous pacing systems remains to be determined,[17] and will likely depend in large part on the evolution of feasibility and ease of multichamber leadless stimulation. Long-term follow-up will need to verify device performance, including the projected battery longevity, stable stimulation thresholds, adequate sensing, and the safety of extraction, if needed.[9] The fate of these devices after reaching end of service remains undetermined. Whether they will remain in place and be turned off, or extracted during implantation of replacement pacing systems (leadless or traditional) is unknown at this point. The perfused cadaveric human heart can fit up to 3 Micra devices along the RV septum.[18] Conceivably, because a

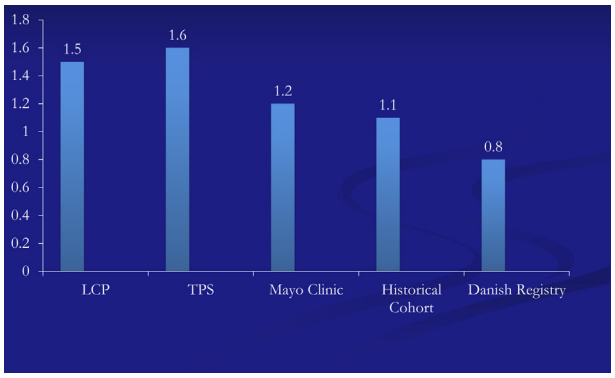

Figure 4. Pericardial effusion rate with leadless and transvenous pacemakers.[1,2,10,12] Adapted and modified from Medtronic training (new implanters) slides.

human heart could fit multiple devices, a strategy to manage patients with sequential leadless devices over a long interval appears possible, if not reasonable. We know little about the feasibility and risks of extracting chronically implanted leadless pacing systems. They can be extracted using traditional snares[19]; however, the ease and safety of extraction of a device implanted long term might be difficult because of near-complete endothelialization of the pacing system against the myocardium.[20–22]

Disclosures

Dr. El-Chami is a Consultant for Medtronic and Principle Investigator to Micra Post Approval Study. The other authors have no conflicts of interest to disclose.

1. Reddy VY, Exner DV, Cantillon DJ, Doshi R, Bunch TJ, Tomassoni GF, Friedman PA, Estes NA 3rd, Ip J, Niazi I, Plunkitt K, Banker R, Porterfield J, Ip JE, Dukkipati SR, Investigators LIS. Percutaneous implantation of an entirely intracardiac leadless pacemaker. *N Engl J Med* 2015;373:1125–1135.
2. Reynolds D, Duray GZ, Omar R, Soejima K, Neuzil P, Zhang S, Narasimhan C, Steinwender C, Brugada J, Lloyd M, Roberts PR, Sagi V, Hummel J, Bongiorni MG, Knops RE, Ellis CR, Gornick CC, Bernabei MA, Laager V, Stromberg K, Williams ER, Hudnall JH, Ritter P; Micra Transcatheter Pacing Study Group. A leadless intracardiac transcatheter pacing system. *N Engl J Med* 2016;374:533–541.
3. Sperzel J, Burri H, Gras D, Tjong FV, Knops RE, Hindricks G, Steinwender C, Defaye P. State of the art of leadless pacing. *Europace* 2015;17:1508–1513.
4. Miller MA, Neuzil P, Dukkipati SR, Reddy VY. Leadless cardiac pacemakers: Back to the future. *J Am Coll Cardiol* 2015;66:1179–1189.
5. Sperzel J, Khairkhahan A, Ligon D, Zaltsberg S. Feasibility, efficacy and safety of percutaneous retrieval of a leadless cardiac pacemaker in an in vivo bovine model. *Europace* 2013;15(Suppl 2):859.
6. Reddy et al., Worldwide clinical experience of the retrieval of leadless cardiac pacemakers, HRS Poster Session, HRS 2016. Available at: http://ondemand.hrsonline.org/common/media-player.aspx/26/35/1913/14605. Accessed on November 21, 2016.
7. Reddy VY, Knops RE, Sperzel J, Miller MA, Petru J, Simon J, Sediva L, de Groot JR, Tjong FV, Jacobson P, Ostrosff A, Dukkipati SR, Koruth JS, Wilde AA, Kautzner J, Neuzil P. Permanent leadless cardiac pacing: results of the LEADLESS trial. *Circulation* 2014;129:1466–1471.
8. Knops RE, Tjong FV, Neuzil P, Sperzel J, Miller MA, Petru J, Simon J, Sediva L, de Groot JR, Dukkipati SR, Koruth JS, Wilde AA, Kautzner J, Reddy VY. Chronic performance of a leadless cardiac pacemaker: 1-year follow-up of the LEADLESS trial. *J Am Coll Cardiol* 2015;65:1497–1504.
9. Link MS. Achilles' lead: will pacemakers Break free? *N Engl J Med* 2016;374:585–586.
10. Kirkfeldt RE, Johansen JB, Nohr EA, Jorgensen OD, Nielsen JC. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. *Eur Heart J* 2014;35:1186–1194.
11. Udo EO, Zuithoff NP, van Hemel NM, de Cock CC, Hendriks T, Doevendans PA, Moons KG. Incidence and predictors of short- and long-term complications in pacemaker therapy: the FOLLOWPACE study. *Heart Rhythm* 2012;9:728–735.
12. Mahapatra S, Bybee KA, Bunch TJ, Espinosa RE, Sinak LJ, McGoon MD, Hayes DL. Incidence and predictors of cardiac perforation after permanent pacemaker placement. *Heart Rhythm* 2005;2:907–911.
13. Auricchio A, Delnoy PP, Regoli F, Seifert M, Markou T, Butter C; collaborative study group. First-in-man implantation of leadless ultrasound-based cardiac stimulation pacing system: novel endocardial left ventricular resynchronization therapy in heart failure patients. *Europace* 2013;15:1191–1197.
14. Auricchio A, Delnoy PP, Butter C, Brachmann J, Van Erven L, Spitzer S, Moccetti T, Seifert M, Markou T, Laszo K, Regoli F; Collaborative Study Group. Feasibility, safety, and short-term outcome of leadless ultrasound-based endocardial left ventricular resynchronization in heart failure patients: results of the wireless stimulation endocardially for CRT (WiSE-CRT) study. *Europace* 2014;16:681–688.
15. Tjong FV, Brouwer TF, Kooiman KM, Smeding L, Koop B, Soltis B, Shuros A, Wilde AA, Burke M, Knops RE. Communicating Antitachycardia pacing-Enabled leadless pacemaker and subcutaneous implantable defibrillator. *J Am Coll Cardiol* 2016;67:1865–1866.
16. Tjong FV, Brouwer TF, Smeding L, Kooiman KM, de Groot JR, Ligon D, Sanghera R, Schalij MJ, Wilde AA, Knops RE. Combined leadless pacemaker and subcutaneous implantable defibrillator therapy: feasibility, safety, and performance. *Europace* 2016;18:1740–1747.
17. Gold MR. Are leadless pacemakers a niche or the future of device therapy? *J Am Coll Cardiol* 2015;65:1505–1508.
18. Omdahl P, Eggen MD, Bonner MD, Iaizzo PA, Wika K. Right ventricular anatomy can accommodate multiple Micra transcatheter pacemakers. *Pacing Clin Electrophysiol* 2016;39:393–397.
19. Gerdes C, Nielsen JC. Retrieval of Medtronic Micra transcatheter pacing system after tether removal. *Europace* 2016;18:1202.
20. Kypta A, Blessberger H, Kammler J, Lichtenauer M, Lambert T, Silye R, Steinwender C. First autopsy description of changes 1 year after implantation of a leadless cardiac pacemaker: Unexpected ingrowth and severe chronic inflammation. *Can J Cardiol* 2015. http://dx.doi.org/10.1016/j.cjca.2015.12.028 [Epub ahead of print].
21. Tjong FV, Stam OC, van der Wal AC, Beenen LF, Bouma BJ, de Groot JR, Wilde AA, Knops RE. Postmortem histopathological examination of a leadless pacemaker shows partial encapsulation after 19 months. *Circ Arrhythm Electrophysiol* 2015;8:1293–1295.
22. Borgquist R, Ljungstrom E, Koul B, Hoijer CJ. Leadless Medtronic Micra pacemaker almost completely endothelialized already after 4 months: first clinical experience from an explanted heart. *Eur Heart J* 2016;37:2503.