



Leadless pacemakers: a contemporary review

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1 Introduction

Over one million cardiac pacemakers are implanted every year worldwide,^[1] of which approximately 200,000 are implanted in the United States alone.^[2] Combined with an aging population and increasing pacing indications, these numbers are expected to grow. Since the first pacemaker implantation in 1950s, cardiac pacemaker technology has rapidly advanced. Reduction in generator size, increased battery longevity, quality of pacemaker leads, algorithmic and rate responsive programming—all have revolutionized and transformed the implantation and management of transvenous cardiac pacemaker (TV-PPM).

Despite these advances, the potential for complications and technical failure always necessitates consideration. Short-term complications, which have been reported to be as high as 12%,^[3] are typically related to the presence of a transvenous lead and or subcutaneous pocket. These complications include pneumothorax, cardiac perforation, lead dislodgement, and pocket infection or hematoma. Long-term complications are also related primarily to the pacing lead and subcutaneous pocket, and include pocket infection, tricuspid regurgitation, venous obstruction, lead fractures and insulation failure. In addition, development of lead related endocarditis is a significant concern, with mortality rates reported between 12%–31%.^[4–6] Some Studies have shown that long-term complications are primarily related to lead failure, identifying it as the weakest component of the current pacing system.^[3,7]

Data obtained from the Truven MarketScan database, which tracks Medicare and US health care claims, showed a 15%–16% complication rate at three years among 72,701 patients with TV-PPM, representing a significant economic burden to both the patient and healthcare system.^[8]

Leadless pacemakers were initially conceptualized in the 1970s^[9] and successfully implanted in dogs using a mercury

battery powered capsule. With advanced battery technology, communication capability, and catheter-based delivery systems leadless pacemakers became a reality. In this paper, we will discuss the current leadless pacing systems focusing on their pros and cons as compared to traditional TV-PPM.

2 Leadless pacemaker

Two leadless pacing systems are currently available: the Micra transcatheter Pacing system (Medtronic) and the Nanostim Leadless Cardiac Pacemaker (St. Jude Medical). Both systems provide right ventricular sensing, pacing, and rate responsiveness. While both of these pacing systems are delivered percutaneously via the femoral vein through a catheter delivery system, they differ with respect to size, fixation to the myocardium, and responsiveness. Characteristics of the two devices are shown in Table 1.

The Micra Transcatheter Pacing system received FDA approval in April 2016, while the Nanostim is still awaiting FDA approval. The Nanostim recently had two major recalls: one due to premature battery failure and the second due to spontaneous detachment of the docking button (a feature designed to allow retrieval of the Nanostim).

Table 1. Comparison of Nanostim and Micra Pacing System characteristics.

Characteristics	Nanostim	Micra
Length, mm	41.4	25.9
Volume, cm ³	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, yrs	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 from El-Chami, *et al.*^[31] with permission. *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.

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Implantation technique for both devices are similar—both utilize a percutaneous catheter based approach to introduce the device into the right ventricle. The introduced sheaths for the Nanostim measure 18 French (inside)/21 French (outside), while the Micra has a 23 French (inside) /27 French (outside). The Micra uses nitinol tines to affix to the myocardium, while the Nanostim uses an active fixation screw in helix (Table 1, Figure 1 and Figure 2). After determining stability and electrical thresholds, the pacemaker is released from the catheter. Interrogation of the device differs: the Micra uses conventional radiofrequency communication, while the Nanostim uses conductive communication of ECG electrodes. Both provide rate responsiveness—the Micra uses a 3 axis accelerometer,^[10] while the Nanostim uses a temperature sensor. Currently, only the Nanostim has a dedicated catheter for retrieval via a snare. However, the Micra has been able to be retrieved using the introducer sheath and gooseneck snares. A recent retrospective study showed successful retrieval of the Micra device, the longest being 95 days from implant.^[11]



Figure 1. A Nanostim and a Micra pacemaker side by side.

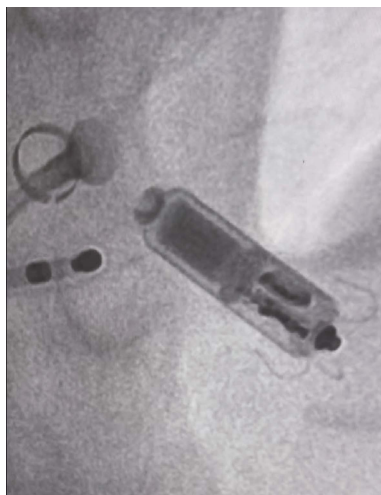


Figure 2. Fluoroscopy of Micra pacemaker with nitinol tines affixed to myocardium.

3 Clinical data

The LEADLESS trial,^[12] the first human trial for leadless pacing, used the Nanostim device. This trial enrolled 33 patients who qualified for single chamber right ventricular pacing. Successful implantation was achieved in 32 of 33 (97%) patients. The procedure was aborted in one patient due to cardiac perforation and tamponade. Only 5 (15%) of patients required more than one device. The complication free rate at 90 days was 94% (31/33) with either improved or stable pacing measurements. At one year follow up, there was stable electrical performance of the leadless pacemaker, appropriate rate responsive histograms, and no device related complications.^[13]

A second study, the LEADLESS II,^[14] was a non-randomized, prospective study which enrolled 527 patients. Successful implantation occurred in 507 of 526 (95.8%) patients, with most patients (70%) not requiring device repositioning. Device related adverse events occurred in 6.5% of patient. Pericardial effusion occurred in 1.5% of patients, the majority requiring an intervention. Vascular complications occurred in 1.2% of patients. Within the first month, there were 6 device dislodgements—four in the pulmonary artery, and two in the femoral vein, where were all retrieved successfully percutaneously. Another 0.8% of patients underwent device retrieval at a mean of 160 days for elevated pacing thresholds, worsening heart failure, and elective explantation.

Recently, a higher than expected battery failure rate was discovered in 7 of 1423 (0.5%) of patients who had received the device. Abrupt battery failure in these devices resulted in loss of communication and pacing. There has been no evidence of any failure in the Micra devices. Currently, no Nanostims are implanted due the two major recalls mentioned above.

The Micra investigational device exemption (IDE) prospective study evaluated the Micra pacemaker^[15] in patients who met Class I or II guideline indications for permanent VVI pacing.^[16] Micra implantation was successful in 719 of 725 (99.2%) of patients. Device complications occurred in 3.4% of patients, including cardiac perforation (1.5%), vascular complications (0.7%), venous thromboembolism (0.3%), and increased pacing thresholds (0.3%). There was one death, which was not procedural related, but due to metabolic acidosis and renal failure. There were no device dislodgements. At 6 months, major complications were seen in 4% of patients. This trial included a pre-specified historical cohort of patients implanted with single lead TV-PPM. The Micra system was associated with a 48% reduction in major complications as compared with the TV-PPM cohort.

The Micra Post Approval Registry (PAR) was also a prospective, non-randomized, multicenter registry designed to evaluate the safety and effectiveness of the Micra in a real world setting.^[17] The study is currently active, with enrollment projected at 1830 patients. An analysis of the first 795 patients was recently published. The indications for pacing were the same as the previous Micra IDE study. Patients were mostly male (62.3%) with an average age of 75.1 ± 14.2 years. In addition, 13.1% of patients had a previously implanted cardiac device. Device implantation was successful in 792 of 795 (99.6%) patients. Within the first 30 days, there were a total of 13 complications in 12 patients. There were 22 deaths, with only one attributed to the procedure: a patient with aortic valve disease who developed pulmonary edema and could not be resuscitated. This patient had no evidence of pericardial effusion and had a normal device function.

Five out of 795 patients (0.63%) developed a pericardial effusion in the Micra PAR. This represents a lower rate of perforation as compared to the Micra IDE trial (1.5%). The Micra pacemaker was placed in a non-apical location in 60% of patients (predominantly septal) in the Micra PAR, while 66% of patients had an apically placed Micra in the original IDE study. This tendency to avoid an apical location could explain the lower rate of perforation seen in the Micra PAR.

4 Comparison of Micra versus Nanostim

There is no head to head comparison between the Micra and Nanostim. Both the Micra and Nanostim had similar complications rates for vascular injury and pericardial effusion (1.5%). However, in the Micra Post Approval Study,^[17] the rate of pericardial effusion was lower occurring in 5 of 795 (0.63%), with two requiring pericardiocentesis.

Device dislodgment was higher in the Nanostim as compared to the Micra pacemaker. In the LEADLESS trial,^[12] no device dislodgements were identified. However, there were six device dislodgements in the LEADLESS II trial:^[14] four in the pulmonary, two in the femoral vein—all were successfully retrieved. In comparison, there were no dislodgements in the Micra IDE trial (one was retrieved due to rise in threshold, without overt macro-dislodgement) and only one dislodgment occurred in the Micra Pacing Post Approval study. This higher rate of dislodgement in the Nanostim could be related to the difference in the fixation mechanism between the two devices (Table 1 and Figure 1).

5 Comparison to Traditional Systems (Figures 3 & 4)

Currently, there are no trials comparing leadless pace-

makers to single chamber ventricular (VVI) pacemakers. However, a review^[18] recently performed a literature search of VVI pacemaker cohorts ($n = 14,330$), and compared this to the three leadless pacemaker trials ($n = 1284$)^[12,15,18] by short term (< 2 months) and long term (> 2 months) complications. The short term complication for transvenous pacemaker (4.0%) was lower than leadless pacemaker (4.8%). Acute lead (0.4%) versus device dislodgements (0.5%) were comparable, while higher risk of cardiac perforation were higher in the leadless group when compared to the VVI cohort (1.5% vs. 0.1%). A meta-analysis comparing cardiac perforation in both transvenous and leadless pacemakers showed the incidence of lead perforation in TV-PPM systems to be lower (range 0 to 6.37%, mean 0.82%) compared with leadless pacemaker (1.5%).^[19] However, both operator experience and developing technology likely contributed to this finding. This is evident with the lower rate of complications in the Micra PAR as compared to the Micra IDE study. Specifically, the lower rate of perforation in the registry is reflective of a learning curve as expected with any new technology. With the exception of the apparent higher rate of perforation with leadless pacemakers, the total rate of complications appears to be lower with leadless pacemakers as compared to TV-PPM (Figures 3 & 4).

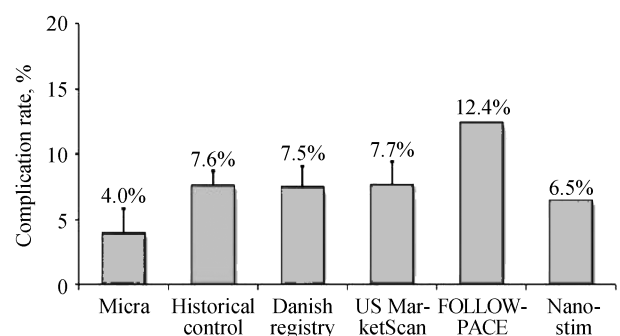


Figure 3. Complication rate of leadless as compared to transvenous pacemakers from multiple published trials.^[3,7,8,14,15]

Adapted and modified from El-Chami, *et al.*^[31] with permission.

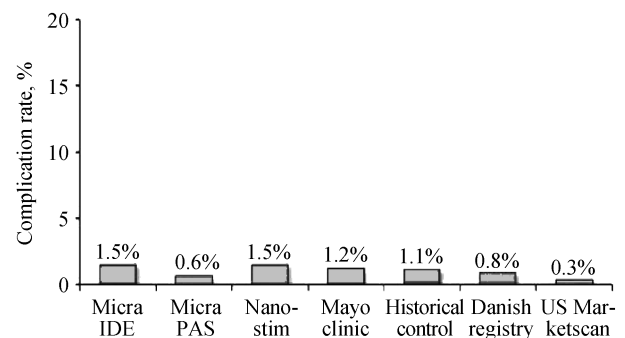


Figure 4. Rate of pericardial effusion with leadless vs. transvenous pacemakers as reported from multiple published trials.^[3,8,14,15,17,32]

Adapted and modified from El-Chami, *et al.*^[31] with permission.

The proposed advantage of leadless pacemakers is to avoid long term complications—primarily with respect to lead and pocket complications. Preliminary reports of long-term performance and complications are promising. A recent report from the Micra study compared matched cohorts of transvenous pacemakers, demonstrating 48% lower complications and 47% less hospitalizations at one year, driven by an 82% decrease in pacemaker revision procedures in the Micra group.^[20] Similarly, Nanostim implanted patients were compared to matching cohorts, showing 71% reduction in complications up to two years.^[21] To this date, the longest follow up was recently published^[22] for three year outcomes from the LEALDESS trial.^[12] Freedom from complications were 89.9% at 40 months follow up. Two of the patients had procedure related events; the third patient experienced loss of pacing and communication at 37 months due to battery failure, as previously described. While the current data on long-term performance are limited, further follow up is needed to ensure safety and durability of these novel pacing systems.

6 Clinical applicability and future innovation

Leadless pacing offers an innovative approach for cardiac pacing while avoiding the pitfalls of transvenous pacemaker. In patients who require atrioventricular node ablation for uncontrolled atrial fibrillation, leadless pacing has been shown to be a feasible alternative.^[23,24] In addition, there are report of using leadless pacemaker in conjunction with subcutaneous defibrillator for antitachycardia pacing or independent pacing.^[25,26] However, the downside of chronic right ventricular pacing are well known,^[27,28] including atrioventricular and mechanical dysfunction, leading to heart failure.

A wireless cardiac system (WiCS-LV) for left ventricular pacing is currently under investigation.^[29,30] This system uses a pulse generator, which is placed subcutaneously at the lateral thorax. This communicates with a leadless pacing electrode, which is placed in the left ventricular endocardium, via acoustic energy. This pacing electrode is able to convert the acoustic energy to an electric pacing impulse. The system is compatible with traditional transvenous systems and leadless pacemaker. The first trial, the WiSE-CRT, demonstrated successful implantation in 13 of 17 (76.4%) patients, but had significant complications, including myocardial perforation with hemopericardium (18%), with one leading to death.^[31] A follow up study, the SELECT-LV study, had successful implantation in 97.1% of patients without significant procedural complications. Further clinical trials will be needed to demonstrate the feasibility of this pacing modality.^[32]

Currently only single chamber leadless pacemakers are available. Future development of leadless VDD systems, dual chamber systems and cardiac resynchronization therapy will allow the expansion of leadless pacing to a broader group of patients.

7 Conclusions

Leadless pacemakers have shown both safety and efficacy in the short term and intermediate follow-up as an alternative to transvenous pacemakers. This technology shows promise in the field of cardiac pacing. As this technology continues to mature, randomized clinical trials comparing this technology to traditional transvenous pacemakers are needed to confirm or refute the perceived advantage of this technology. In addition, an approach to end of service management and retrieval of chronically implanted devices still need to be addressed. However, the early positive experience with leadless pacing systems supports the wider use of this novel technology in a select group of patients.

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