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Review Article

Leadless pacemakers – The path to safer pacing?

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ABSTRACT

Endocardial transvenous permanent pacemakers (TVPs) are a mainstay within cardiology and used to treat a range of bradyarrhythmias. However, their use is associated with potential complications both at the time of implantation and longer term. The concept of a leadless pacemaker, where a self-contained device is placed within the right ventricle, has obvious attractions. Two leadless systems have been developed, though only one is currently available. Results from clinical trials have been promising but a number of hurdles need to be circumvented before leadless devices can usurp TVPs. At present, use is restricted to specialist centres, for a limited indication and for patients in whom conventional implantation is contraindicated. This article provides a contemporary critique of design types, evidence base and existing limitations of this nascent technology.

1. Introduction

Over the last 60 years, use of endocardial transvenous permanent pacemakers (TVPs) has protected patients from symptomatic bradyarrhythmias. As with any invasive procedure, the potential exists for complications. In the context of transvenous systems, these occur more frequently than generally acknowledged with a recent nationwide cohort study quoting an incidence of 9.5%.[1]

Insertion of a TVP involves fashioning of a pocket most commonly in the pre-pectoral region for the generator, followed by central venous access to enable passage of the pacing leads into the heart. Once within the cardiac chambers, the leads are positioned under fluoroscopic guidance and fixed to the myocardium, either passively or actively. Complications can arise at any of these steps; infection, haematoma and skin erosions can arise from the pocket, whilst pneumothorax, haemothorax or venous stenosis can occur during or after central venous cannulation. Finally, the leads themselves are susceptible to dislodgement, fracture or insulation failure. An entirely self-contained intracardiac pacemaker device may circumvent these risks. In this paper, we will discuss the design types of leadless pacing systems, their evidence base and limitations.

2. Design types

Two types of leadless pacemaker have been designed for use in patients: the Nanostim LCP (Abbott) and the Micra Transcatheter Pacing System (Medtronic). They both consist of an integrated generator and receiver, which is much smaller than a TVP generator [Table 1], and can be directly delivered to the endocardium of the right ventricle via the femoral vein using a catheter-based system. However, the Micra is shorter and wider, with the subsequent requirement for a larger diameter delivery sheath (27-French) compared to the Nanostim (18-French). Nanostim utilises an active screw-in helix, whereas Micra incorporates four self-expanding nitinol tines that enable fix to the trabeculated myocardium. Both systems operate as VVI(R) devices, meaning that they can sense and pace the ventricle only whilst also providing a rate response facility. In contrast, as TVPs can have a lead in both the atrium and ventricle, they offer the capability to sense and pace both as well as providing rate response (DDD(R)). The Micra and Nanostim devices have battery longevity estimated to be in the order of 10 years, and both are equipped with a proximal groove to enable potential extraction using a snare.

Abbreviations: AV, Atrioventricular; DDD(R), Pacing and sensing capabilities in both the atrium and ventricle, with a rate response facility; IDE, Investigational device exemption; PFO, Patent foramen ovale; PAR, Post-Approval Registry; RCT, Randomised controlled trials; TVP, Transvenous permanent pacemaker; VVI(R), Ventricle pacing and sensing with inhibition of pacing output, with a rate response facility; VDD, Ventricle pacing with dual sensing and dual response to sensing; VT, Ventricular tachycardia.

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Table 1
Comparison of characteristics of pacing devices.

Parameter	Transvenous Pacemaker	Nanostim	Micra
Dimensions (mm)	42.5 × 50.8 × 7.4	42 × 6.0	25.9 × 6.7
Weight (g)	22.5	2.0	2.0
Delivery sheath size (Fr)	–	18	27
Fixation	Active or passive	Active	Passive
Polarity	Bipolar or unipolar	Bipolar	Bipolar
Generator longevity (years)	14	10–15	5–10
Pacing mode	VVI(R) or DDD(R)	VVI(R)	VVI(R)

3. Study data

3.1. Nanostim

LEADLESS was the first human trial of leadless pacemakers, consisting of 33 patients.[2] The implantation success rate was 96.9%, with complication-free success rate of 93.9% at 3 months and stable device performance. At 12-month follow-up, there were no further device-related complications and stable device performance.[3]

LEADLESS II was a larger, non-randomised study to provide data on long-term effectiveness enrolling 526 patients.[4] Results were encouraging, with a 95.8% implantation success rate. Freedom from complications was 93.3% at 6-month follow-up. Complications included pericardial effusion in 1.6% and femoral vein complications in 1.1%. There was device dislodgement with embolisation in 1.1%, though they were all successfully retrieved percutaneously, and elective device retrieval for elevated pacing thresholds in 0.8%. There were two procedure-related deaths, one due to a cerebrovascular accident after successful surgery for acute perforation and the other after inadvertent placement in the left ventricle through a patent foramen ovale (PFO) that had to be repositioned in the same procedure.

Subsequently the parent company put a voluntary hold on implantation of the Nanostim after receiving seven reports of 'lost telemetry and pacing output' but fortunately no associated patient injury. In the end, of 1423 implantations worldwide, there were 34 battery failures (2.4% of cohort). Retrieval was successful in 90.4% of attempts; however, in six cases the docking button was inaccessible and in one case the docking button detached from the device during retrieval. In addition, the procedure was complicated in one case by arteriovenous fistula and in another by the migration of the docking button into the pulmonary artery.[5]

3.2. Micra

The Micra Investigational Device Exemption (IDE) study was a prospective, single-arm study that assessed effectiveness in 725 patients.[6] Early performance showed 99.2% implant success rate, with low and stable capture thresholds in 98.3% of patients. At 6 months, 96.0% remained free from major sequelae. Complications included pericardial effusion in 1.5% of patients, femoral vein complications in 0.7% and elevated pacing thresholds requiring replacement in 0.3%. There were no device dislodgements but one death from metabolic acidosis in a dialysis-dependent patient that may have arisen from the prolonged procedural time.[7]

The prospective non-randomised multi-centre registry of Micra implants (Micra Post-Approval Registry (PAR)) now consists of 1817 patients and has shown continued implantation success rate (99.1%) with stable pacing parameters through 18 months of follow-up.[8]

There was a low complication rate of 2.26% at 12 months, with 89% of complications occurring in the first 30 days post-implant. The incidence of pericardial effusion was lower than the original study (0.8%) and may reflect the preference in the training programme for implanting the device on the septal aspect of the right ventricle for the perceived benefit of reducing risk of perforation. This led to an increase in the percentage of implants to a septal position versus the IDE study (52% vs 33%). There were static rates of puncture site complications (0.6%) and elevated pacing thresholds requiring replacement (0.6%). There was one case of dislodgement without embolisation (in the proximity of the papillary muscle) and five procedure-related deaths. Of these, two related to cardiac perforation, one related to severe aortic stenosis and pulmonary oedema (albeit normal device function) and one due to retroperitoneal haemorrhage in a 92-year-old female with a low body mass index.

3.3. Nanostim vs micra

There have been no direct comparisons between the two primary designs of leadless pacemakers. Data from clinical trials have suggested high successful implantation rates and satisfactory pacing parameters for both systems.

The Micra PAR cohort showed that the movement towards septal placement led to a higher rate of successful implantation and a lower rate of pericardial effusion. In addition, there were lower rates of elevated pacing thresholds and no reports of device dislodgement with embolisation [Table 2].

Finally, battery failure has been the key adverse event undermining the safe use of the Nanostim system, and the voluntary hold on its implantation leaves the Micra as the only commercially available leadless pacemaker model.

3.4. Comparison with TVPs

There are no randomised controlled trials (RCT) directly comparing leadless pacemakers to single chamber TVPs. Registry data for both designs have been compared to TVP data sets.

A propensity score-matched analysis of 440 patients showed a complication rate of only 0.9% in patients in the LEADLESS cohort compared to 4.7% in a contemporary prospective multi-centre registry of VVI pacemakers at 800 days follow-up, when excluding pacemaker advisory-related complications.[9]

Table 2
Comparison of reported adverse events from the LEADLESS and Micra PAR cohorts.

Adverse Events	Nanostim in LEADLESS II cohort and in subsequent studies where it was retrieved (percentage, no. of patients)	Micra in Micra PAR cohort (percentage, no. of patients)
Pericardial effusion	1.6 [8/526]	0.8 [14/1817]
Femoral vein complications	1.1 [6/526]	0.6 [11/1817]
Pacing threshold elevation requiring replacement	0.8 [4/526]	0.6 [11/1817]
Device dislodgement	1.1 [6/526]	0.1 [1/1817]
Battery failure	2.4 [34/1423]	0.0 [0/1817]
Procedure-related death	0.4 [2/526]	0.2 [5/1817]

The Micra PAR cohort has been compared to a registry data set of 2667 patients from six Medtronic trials of dual chamber pacemakers (with complications related to the right atrial lead of the TVPs excluded). This comparison showed a 63% reduction in major complications from 7.6% to 2.7% at 12 months, primarily driven by a 74% relative risk reduction in system revisions and 71% relative risk reduction in hospitalisations.[8] However, 2401 of the TVPs had been implanted before 2008 whereas the Micra cohort were implanted between 2015 and 2018. A fairer comparison of complication rates in contemporary practice would require a registry of TVPs implanted from 2015 onwards.

4. Device limitations

Firstly, the system can currently only be utilised for sensing and stimulating the right ventricle. The inability to pace both chambers of the right heart leaves patients susceptible to atrioventricular (AV) dyssynchrony, which can adversely affect cardiovascular physiology.[10] As such, dual chamber TVPs become the default to preserve physiological cardiac contractility, potentially restricting the use of leadless pacemakers to patients with chronic atrial fibrillation who require only isolated ventricular pacing. Notably, the recent MARVEL study has suggested a possible route to AV synchrony for leadless systems via utilisation of custom software that detects atrial contraction using a 3-axis accelerometer and supports a VDD mode (ventricle paced, dual sensing and dual response to sensing).[11] However, whilst the headline figure from this study states that the average proportion of patients achieving atrioventricular synchrony (AVS) was 87%, it should be noted that almost half of the study population had intrinsic conduction; amongst the patients with high-degree block, the rate of AVS was only 80%. Looking back at historical studies comparing dual-chamber to single chamber pacing, such as Pacemaker Selection in the Elderly (PASE),[12] Canadian Trial of Physiologic Pacing (CTOPP),[13] and Mode Selection in Sinus Node Dysfunction (MOST),[14] around one-third of the patients crossed over from VVI to DDD mode due to the development of pacemaker syndrome as a result of AV dyssynchrony. As such, the rate of AVS achievable by leadless pacing as demonstrated in MARVEL would be inadequate for most patients, other than sedentary or elderly individuals whose heart rate rarely exceeds 90 bpm. Overall, whilst the results of the MARVEL study highlight a promising avenue for future development in the field of leadless pacing, it also demonstrates that the technology has a long way to go before it can be comparable to TVP.

Secondly, trial results have been extracted from non-randomised studies, with a paucity of data on long-term sequelae and, as highlighted, no direct comparisons between the two leadless pacing systems or each against TVP. Ongoing registries should deliver long-term outcome data and provide greater clarification regarding true battery longevity.

Thirdly, when battery voltage reaches end-of-life, there is no data on explanting a system that has been in place longer than 3 years. One potential option is to program 'off' the device, with up to two further devices accommodated within the ventricle.[15]

Finally, the economic aspect of leadless pacing needs to be addressed. In a recent survey encompassing a number of European centres, the most frequently cited reason for not implanting leadless pacemakers was the high cost of the device.[16] Indeed, it is estimated that leadless pacemakers cost 7–10 times as much as TVPs. Whether a proportion of this excess cost becomes amortised due to the development of fewer long-term complications remains to be seen.

5. Conclusion

The development of leadless pacemakers marks a potential paradigm shift in cardiac pacing, and the theoretical advantage to reduce complication rates is clear. We await more data from the Micra PAR and LEADLESS registries to give answers on battery longevity and long-term outcomes.

The current device limitations and lack of long-term evidence prohibit more generalised use of leadless pacemakers and the voluntary hold on Nanostim system implantation threatens to slow technological progression. Nonetheless, the preliminary data are favourable, and this highlights the need for further research, specifically RCTs, to truly gauge the merit of leadless technology versus TVPs.

Declaration of competing interest

All authors have none to declare.

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