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Leadless pacemakers – a panacea for bradyarrhythmias?

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Take Home Messages

- The topic is important because leadless pacemakers may revolutionise the field of device therapy.
- This editorial provides an overview of landmark trials and critically appraises benefits and limitations.
- Going forward, increased procedural familiarity and data on long-term outcomes shall inform clinical practice.
- My opinion is that it may be deployed as an alternative strategy in challenging subcohorts where traditional approaches have failed.

Why may leadless systems be required?

"Where the cessation of vital action is very complete, and continues long, we ought to inflate the lungs, and pass electric shocks through the chest: the practitioner ought never, if the death has been sudden, and the person not very far advanced in life, to despair of success till he has unequivocal signs of real death (Allan Burns, 1809)."

For more than 50 years, the use of endocardial transvenous permanent pacemakers has revolutionised management of bradyarrhythmias. The contemporary era has heralded significant advances in battery longevity, lead designs and device programming capabilities [1]. Modern pacemakers have enhanced capabilities and increasingly complex features, such as auto-programmability, haemodynamic sensors and remote monitoring.

However, these traditional transvenous systems have inherent limitations. Device-related adverse events occur more frequently than generally acknowledged, with a recent nationwide cohort study quoting an incidence of approximately 10% [2]. Procedural sequelae from pocket formation include infection, haematoma and skin erosions [3]. Transvenous access may inadvertently lead to pneumothorax or vein stenosis, and chronic lead positioning can cause vein obstruction and tricuspid regurgitation. The leads themselves are susceptible to dislodgement, fracture or

insulation failure, and this can be associated with major adverse clinical events including angina, congestive cardiac failure and syncope [4].

The transvenous leads are traditionally recognised as the weakest link in pacemaker procedures. This has prompted the pursuit of leadless systems to circumvent this limitation, with the notion of an entirely self-contained intracardiac pacemaker device postulated nearly 50 years ago [5]. Although progress was stagnant for several decades, there has been a resurgence of interest in the wake of technological advancements relating to delivery systems, packaging technology and communication capabilities.

What are the design types?

Broadly speaking, there are two design types for leadless systems: single- and multi-component.

The single-component device consists of an integrated generator and receiver, with sensing and pacing electrodes in a bipolar configuration and contained within a single unit. It is delivered to the endocardium of the right ventricle (RV) via the femoral vein. There are currently two types commercially available for use in humans: the Nanostim LCP (St Jude Medical) and the Micra Transcatheter Pacing System (TPS) (Medtronic). The TPS is typically shorter but wider, with the subsequent requirement for a larger delivery sheath (24-F) compared to the LCP (18-F). LCP utilises an active screw-in helix, whereas TPS incorporates four self-expanding tines that enable fix to the myocardium. LCP has roughly double the estimated battery longevity (10 vs 5 years). Both systems, however, are equipped with a proximal groove to enable potential extraction using a snare. A direct comparison of LCP and TPS devices is provided below (see Table 1).

	LCP	TPS
Delivery sheath size (F)	18	24
Fixation	Helix	Tines
Generator type	Lithium carbon monofluoride	Lithium silver vanadium oxide / carbon monofluoride
Generator longevity (yrs)	10 years	5 years
Pacing mode	VVI(R)	VVI(R)
Energy capacity (mAh)	248	120
Rate modulation	Blood temperature	Accelerometer

Table 1 - Comparison of LCP and TPS single-component devices

Multi-component devices consist of a subcutaneous pulse generator and a small receiver electrode. The generator is implanted in the left lateral thorax and the receiver is adhered to the endocardium of the left ventricle (LV), using a retrograde aortic approach. The device relies upon ultrasound-mediated energy transfer, whereby ultrasonic waves are produced by the generator and converted by the positioned receiver into electric pacing impulses [6].

What does trial data suggest?

A) Single-component

LEADLESS was the first feasibility study using single-component LCP systems [7]. In this prospective study, patients were eligible for study recruitment if they had traditional indications for single-chamber pacing (VVI). The implantation success rate was 97%, with complication-free success rate of 94% at 3 months and stable device performance

measures including pacing threshold, impedance and sensing. This trend was preserved at 12 months, with no documented device-related complications [8]. LEADLESS II was a further, non-randomised study to provide data on long-term effectiveness of LCP systems [9]. There was 96% implantation success rate. Device-related serious adverse events occurred in 7% during 6 month follow-up, and included device dislodgement, cardiac perforation and pacing threshold elevation requiring percutaneous retrieval.

The Micra Transcatheter Pacing System study was a prospective, single-arm study that assessed effectiveness of TPS systems [10]. Early performance showed 99% implant success rate, with low and stable pacing capture thresholds. No major complications were observed at 6 months. Long-term performance assessed over 12 months was consistent with previously reported data, with 96% remaining free from major complications [11].

B) Multi-component

WiSE-CRT was a prospective, observational feasibility study to assess the benefits of multi-component leadless LV pacing in cohorts with guideline indications for cardiac resynchronisation therapy (CRT) [12]. All patients had pre-existing devices. LV function appeared improved at 6 months (31% vs 25%; $p<0.01$). However, there was premature termination of the study in view of safety concerns, as successful device deployment was only achieved in 75% and 3 patients (18%) developed iatrogenic pericardial effusions.

In view of this concern, the delivery system was redesigned to enable atraumatic implantation of the receiver. The subsequent SELECT-LV trial was a prospective, non-randomised multi-centre trial assessing outcomes in those with "failed" conventional CRT [13]. Primary indications for leadless device therapy were challenging coronary sinus anatomy, failure to response to conventional CRT, high coronary sinus pacing thresholds or phrenic nerve stimulation. The procedure was successful in 97% of attempted implants. 66% demonstrated positive Echocardiographic response, defined as ≥ 5% absolute improvement in ejection fraction. Serious procedural events occurred

in 3 patients (9%) at 24 hours, and 8 patients (23%) at 1 month follow-up. Overall, the study suggested potential clinical benefit in an otherwise "failed" CRT population.

What are the benefits?

As inferred, the primary advantage of a leadless pacing system is that it obviates the need for subcutaneous pockets and transvenous leads, with associated cosmetic benefit and reduction of specific procedural sequelae. However, there are additional theoretical advantages. The potential risk of infection may be considered as even lower due to smaller device size, its encapsulation within the heart and higher blood velocities. It is also plausible that peri-procedural radiation exposure to the operator may be reduced because of distance from the image intensifier. Moreover, battery longevity may be comparable with traditional transvenous generators, particularly with the LCP device which has current drain of 1 µA compared to 6 µA for transvenous devices.

A separate argument in favour of leadless devices relates to the advantage of LV endocardial pacing, as opposed to epicardial, in conferring a more physiological sequence of transmural activation. This may have adjunct benefits on inotropy, reducing propensity for dysrhythmias and lowering pacing stimulation thresholds [14]. Multiple studies have observed the benefits of targeting LV lead positioning at the site of greatest delay in ventricular activation [15, 16]. Leadless pacing may enable greater flexibility in this regard as it is not hindered by anatomical restrictions relating to branches of the coronary sinus.

What are the limitations?

Firstly, the system can only be utilised for single-chamber stimulation (i.e. RV), and therefore, cohorts such as those with sinus node dysfunction would be currently ineligible. The absence of atrioventricular synchronicity has established adverse effects on cardiac haemodynamics, though this may be bypassed in part by sensing the P wave via VDD mode.

Trial results have been extracted from non-randomised studies, with a paucity of data on long-term sequelae and no direct comparisons between the two available leadless pacing systems (LCP and TPS). The long-term reliability of rate-responsive features remain equally unclear, as the sensor is located in the intra-ventricular space as opposed to the subcutaneous tissue. Similarly, the chronic effects of ultrasound energy exposure on the subcutaneous tissue and myocardium is unknown, with the risk of inefficient transfer causing accelerated battery depletion.

A separate concern relates to procedural sequelae. Access is reliant on a large calibre venous sheath, with a greater potential for complications relating to femoral access site or catheter manipulation for device deployment within the RV. Indeed, a recent meta-analysis has confirmed a marginally higher risk of cardiac perforation with leadless compared to conventional pacemakers (absolute incidence of 1.5%) [17]. This may relate to the technical challenges associated with a less familiar procedure, with the preformed and fixed bending radius of the delivery sheath making it challenging to reach the RV and deploy the system at the desired point.

A further challenge relates to retrieval of chronically implanted devices, with no data available in humans on systems that have been in place longer than three years. Leadless devices become totally encapsulated with fibrotic tissue, and in this scenario, it has been shown that they can be programmed "off" (OOO) with up to two further devices accommodated within the ventricle [18]. However, this results in a higher region of device interaction with the endocardium which may be pro-arrhythmic.

What is the jury's verdict?

Cardiac pacing has spurred the development of a new bioelectronics technology, with the production of robust systems that are efficacious and clinically effective. A prime example of this paradigm shift is the design of leadless pacing devices. Recent advancements in introducer and device size, fixation strategies, battery recharging and alternate battery sources have optimised the system for clinical use. It is plausible that leadless pacing may be indicated for specific cohorts, for instance those who are non-responsive to traditional CRT or where central venous system damage precludes

traditional access routes. However, there are technical challenges associated with lack of procedural familiarity due to exposure only in isolated tertiary centres. Uncertainty in the field remains unabated and many outstanding questions remain. How should the device be handled at the end of their lifespan? Are they conditionally safe for use in MRI machines? How should patients be managed in the context of systemic infections? A direct comparison of leadless and conventional pacemaker systems is warranted, but a recent propensity score-matched analysis has heralded caution due to increased complication rates (11% vs 5%; p=0.06) [19]. As it currently stands, the jury is still out.

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