A new milestone in pacing therapy...

Leadless cardiac stimulation: ready to take centre stage?

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Summary

Over the past few years, the field of cardiac stimulation has witnessed the accelerated development of leadless cardiac pacing, a technology first conceived almost 50 years ago. Currently, two fully intracardiac devices allow single-chamber right-ventricular stimulation: the Nanostim™ and Micra™ leadles pacemakers. Both are still undergoing long-term study, but only the latter device is commercially available in Switzerland. The field of cardiac resynchronisation therapy is also exploring leadless technology, with the development of the Wireless-CRT system, although its state of development is less advanced. These technologies, though still in relatively early stages, represent initial steps in a revolution in cardiac stimulation.

Key words: leadless pacemaker; intracardiac pacemaker; cardiac pacing; left ventricular endocardial pacing; ultrasound-based cardiac resynchronisation therapy

Introduction

The advent of cardiac stimulation devices has revolutionised the treatment of various cardiac disorders, from syncope to arrhythmias and, more recently, in the field of heart failure. During the twentieth century, several milestones were reached leading to the current state of cardiac stimulation, from the first successful use of an external electrical stimulation device in 1932 by Albert S. Hyman [1] to the first implantable epicardial pacemaker by Rune Elmquist and Ake Senning in 1958 [2]. In parallel, interest in development of transvenous lead systems grew, with the first implantation of a temporary transvenous pacing lead in 1958 by Seymour Furman [3], and, finally, the appearance of the first implantable permanent pacemaker systems with transvenous leads in 1962 [4].

Currently, most cardiac implantable electronic devices consist of a pulse generator implanted in the subcutaneous or submuscular tissue, connected to one or more transvenous leads implanted on the endocardial surface of the right chambers or the coronary sinus. The surgical implantation procedure, though a frequently performed intervention in most centres, can have complications in almost 10% of cases [5, 6]. These include haematoma (2–3%) and infection (approximately 1%) at the pocket site, as well as cardiac perforation (0.4–0.6%), lead dislodgment (2–3%) and pneumothorax (around 2%) following placement of the transvenous leads. Further lead-related concerns after device implantation include fracture, insulation defects, connector problems and infection. Despite great advances in pacemaker and lead technologies, these issues are far from being resolved and may even be growing in importance owing to the increasing number of devices and leads-per-device implanted. Indeed, the morbidity associated with device-related complications remains high, and these complications must be balanced against the potential benefit in this population of often very elderly patients.

Since early on, research has investigated the possibility of dispensing with the leads and external generators altogether as one way potentially to eliminate these issues. The feasibility of intracardiac stimulation devices was demonstrated from as early as 1970, with several reports of successful implantation and short-term function in canine models [7, 8]. Though these devices showed great promise, it was not until more recently that the research community and industry have accelerated the development of human leadless pacemakers. At first, the concept of leadless devices still required the implantation of an extracardiac generator that would transmit wirelessly to an intracardiac receiver, either by ultrasound energy [9–11] or magnetic field-induction energy [12]. However, since 2012, several fully intracardiac devices have been developed and later commercialised for pacing the right ventricle. Leadless cardiac pacing is also being developed in the field of cardiac resynchronisation therapy (CRT). Although the results of CRT therapy have been impressive in carefully selected populations, it is still marred by several major issues, such as a relatively high rate of nonresponders and left ventricular (LV) lead failure. LV endocardial pacing offers the theoretical advantage of a wider selection of pacing sites compared with the highly variable anatomy of the coronary sinus branches, and possibly a greater haemodynamic effect.

Until recently, this required a transvenous approach with passage through the atrial or ventricular septum, but with a high rate of systemic thromboembolism [13]. Thus, wireless left ventricular endocardial pacing is also being developed in order to address these issues.

Figure 1: A. The Nanostim™ Leadless Cardiac Pacemaker (St Jude Medical, Sylmar, CA, USA). *Courtesy of St Jude Medical.*
B. The MicraTM Transcatheter Pacing System (Medtronic, Minneapolis, MN, USA). *Courtesy of Medtronic.*

Table 1: Key features of the Nanostim™ Leadless Cardiac Pacemaker (LCP) and Micra™ Transcatheter Pacing System (TPC) Devices.

Parameter	Nanostim™ LCP	Micra™ TPS
Dimensions (length × width, mm)	41.4 × 5.99	25.9 × 6.7
Volume (cm³)	1	0.8
Weight (g)	2	2
Femoral Introducer size (F) – inner diameter – outer diameter	18 21	23 27
Energy capacity (mAh)	248	120
Fixation mechanism	Screw-in helix + nylon tines	Self-expanding nitinol tines
Rate-response sensor	Temperature	Accelerometer
Estimated Longevity (years) ISO standard* Nominal setting** Real-life estimation***	9.8 14.7 15.0	4.7 9.6 12.5
Telemetry	Conductive	Radio frequency
MRI conditionality	Yes (1.5 T full-body)	Yes (3 T full-body)
Remote monitoring	No	No

*: 100% pacing, 2.5 V, 0,4 ms, 60 bpm
**: 100% pacing, 1.5 V, 0.24 ms, 60 bpm
***: Based on 3-month results of clinical trials (LEADLESS II study [24] and Micra™ TPS Study [18])

Characteristics of the different leadless pacing systems

Right ventricular pacing devices

The first fully intracardiac leadless pacing system to be developed was the Nanostim™ Leadless Cardiac Pacemaker System (St Jude Medical, Sylmar, CA, USA), introduced in 2012 and obtaining the CE mark in 2013. This device was followed by the Micra™ Transcatheter Pacing System (Medtronic, Minneapolis, MN, USA), which obtained CE certification recently in 2015. Both devices remain investigational in the United States.

These devices incorporate the battery and electronic circuit as well as bipolar sensing and pacing electrodes in a small capsule-shaped format that is designed to be implanted directly in the right ventricle (RV) (fig. 1). In terms of function, both pacemakers operate as single-chamber VVI devices with optional rate-adaptive pacing, and both use a bipolar sensing and pacing configuration. They possess steroid-eluting cathode tips to ensure similar maturation compared with standard transvenous devices.

Key differences between both devices are highlighted in table 1. The Micra™ has a shorter, wider profile, thus needing a larger gauge delivery sheath (27 F or 0.9 cm). The device is fixated with the help of four self-expanding nitinol tines that are deployed with retraction of the delivery sheath and anchor the device to the myocardium. In contrast, the Nanostim™ possesses a primary screw-in helix with maximal penetration in the myocardium of 1.3 mm and a secondary mechanism of angled nylon tines. Electrodes in the Micra™ consist of a steroid-eluting cathode tip and a titanium ring. In the Nanostim™, a steroid-eluting disk in the centre of the helix acts as the cathode, and the anode, located more than 10 mm away, consists of the non-coated part of the titanium case. Further differences include the modality of rate adaptive pacing: whereas the Micra™ uses a three-axis accelerometer (with filters to distinguish cardiac motion from patient acceleration), the Nanostim™ relies on a central venous temperature sensor.

The telemetry connection with the Micra™ is established via radio frequency with a standard Medtronic model 2090 Programmer and programming head. With the Nanostim™, the system requires two-way conduction with the help of an external module that acts as the link between a model 3650 Merlin™ Patient Care System Programmer and standard ECG skin electrodes placed on the subject's torso. Signals are transmitted to and from the device via subliminal 250-kHz pulses applied to the skin electrodes that do not interfere with pacemaker function.

Left ventricular pacing system

The ultrasound-based WiCS™ system (Wireless Cardiac Stimulation; EBR Systems, Sunnyvale, CA, USA) has been developed to offer leadless LV endocardial pacing with the use of ultrasound transmission and has recently been granted CE mark approval. The system consists of a subcutaneous pulse generator communicating via ultrasound with a receiver electrode (13.5 × 2.6 mm) implanted in the left ventricle (fig. 2). The receiver converts the ultrasound pulses produced by the generator from acoustic to electrical energy, thus pacing the LV. A conventional pacing device (pacemaker, CRT device or implantable cardiac defibrillator) is necessary in order to synchronise LV pacing with RV pacing, using a programmed 3-ms delay.

Implantation procedures of leadless devices

Right ventricular pacing systems

Both devices can be implanted under local anaesthesia and fluoroscopic guidance. The delivery systems contain a deflectable tip that is directed through the right atrium and into the RV via the tricuspid valve. Ideally, the devices are directed to the apical or apico-septal region. Once in position, the implantation of the Nanostim™ LCP device requires retraction of an extendable protective sleeve, exposing the helix, which is then rotated 1.25 turns, enabling fixation [14]. The Micra™ implantation also requires retraction of a sleeve, thus deploying the four tines, of which at least two should hook into the myocardium for a successful deployment. Once fixated, both devices are undocked, but remain tethered to the delivery system, allowing evaluation of stability and pacing performance, and

Figure 2: The WiCS™ system (Wireless Cardiac Stimulation; EBR Systems, Sunnyvale, CA, USA), consisting of a standard right ventricular pacemaker/defibrillator and a subcutaneous pulse generator communicating via ultrasound with a receiver electrode (magnified) implanted in the left ventricle. *Courtesy of Cambridge Consultants* Image courtesy of EBR Systems.

easy repositioning if necessary. Before final release, the operator performs a "pull and hold" under fluoroscopy, then cuts the tethers, freeing the device. Figure 3 illustrates the implantation procedure of the Micra™ TPS system. Apart from formal training by the manufacturers of the different devices, operators undertaking implantation of leadless devices should be experienced in femoral access as well as cardiac stimulation. It is a significant asset to have experience with electrophysiological procedures, as steering of the catheter relates more to this domain than to manipulation of pacing leads. Furthermore, the physician should ideally be competent in lead extraction, as he or she will be more proficient with large-bore femoral access as well as device retrieval in case of need. Device implantation should ideally be undertaken in an environment with high-quality fluoroscopy such as an electrophysiology or catheterisation laboratory, especially with the Micra™ system as correct visualisation of the four tines is mandatory for adequate device placement.

Wireless cardiac resynchronisation therapy system

The leadless receiver is implanted in the LV endocardium via a retrograde aortic approach, and anchored with the help of three self-expanding nitinol tines. The optimal position of the pulse generator in the WiCS™ system is chosen with use of echocardiography in order to find an appropriate acoustic window. Usually this window is found lateral to the left parasternal region in the fourth to sixth intercostal spaces, the fifth intercostal often being the most appropriate [15].

Current scientific evidence regarding leadless pacing technology

Micra™ Transcatheter Pacing System

After initial feasibility studies performed in animals [16], early results of the Micra Transcatheter Pacing Study have been published recently. This ongoing safety and efficacy study is a worldwide, prospective, multi-centre single-arm study that has recruited 744 patients with a class I or II indication for single-chamber ventricular pacing, of whom 725 underwent an implantation attempt. Preliminary results once the first 60 patients had completed 3 months follow-up were published in 2015 [17] and, more recently, a planned interim analysis of the first 300 patients completing 6 months of follow-up was published [18]. Implantation was successful in 719 patients (99.2%), with a mean procedure time of 34.8 ± 24.1 min, and fluoroscopy time of 8.9 ± 16.6 min, higher than the usual fluoroscopy time (<5 minutes) for a single-chamber transvenous pacemaker. Among the first 140
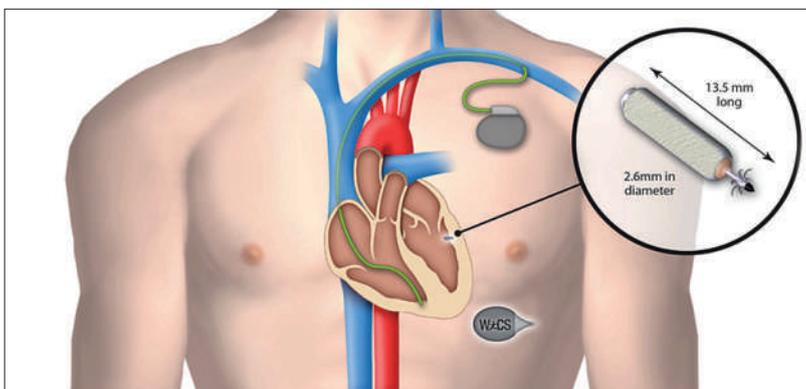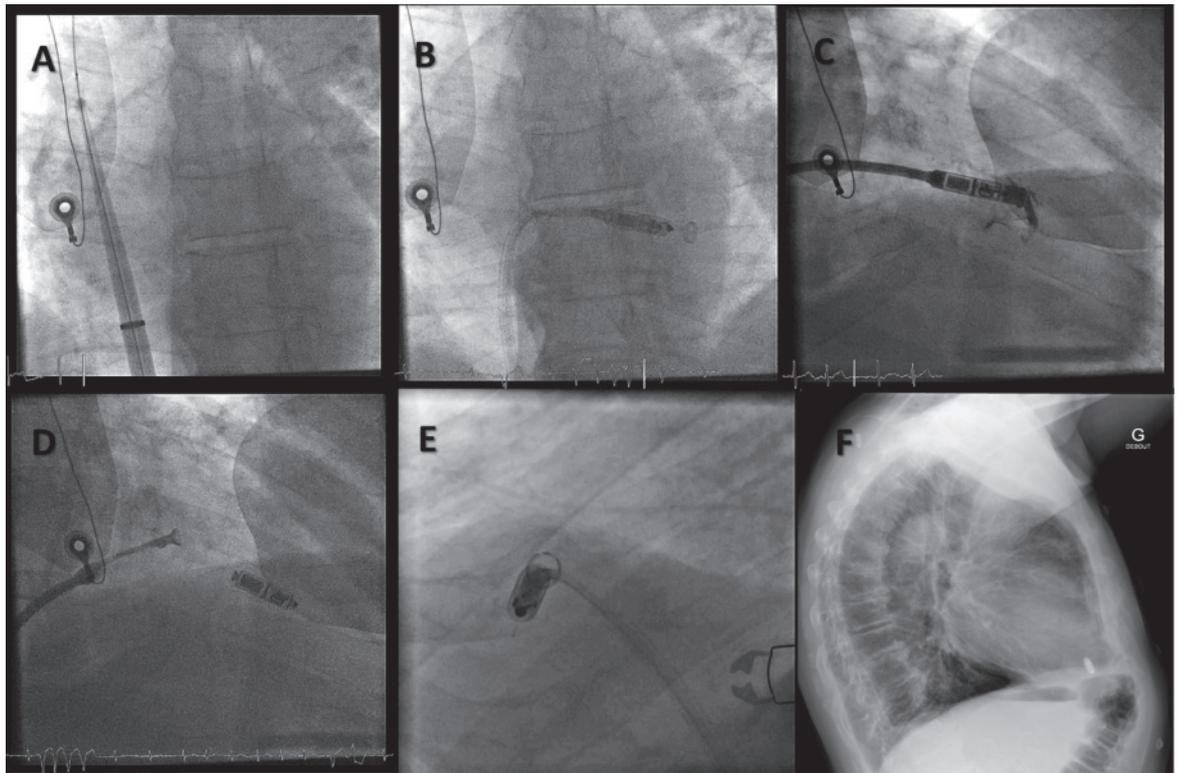
Figure 3: Implantation of a Micra™ system.
A. The delivery system is introduced via the femoral vein into the right atrium via a super-stiff guidewire.
B. The Micra™ unit is introduced into the deflectable delivery system and positioned across the tricuspid valve into the right ventricle.
C. The apical septum is targeted using contrast injection.
D. The delivery sheath is withdrawn, thus deploying the tines into the ventricular wall.
E. A "pull and hold" test is performed, with viewing in multiple planes to verify that at least two of four tines are fixated, and the tether is then cut to free the device.
F. Lateral chest X-ray of the implanted system.

patients, optimal device position was achieved on the first attempt in 59% of patients, and 18.9% required more than two deployments.

With regards to pacemaker efficacy, 98.3% of patients reached the primary efficacy endpoint consisting of a capture threshold <2.0 V at 6 months, without significant (>1.5 V) increase since implantation (p <0.001). Mean pacing threshold value was 0.54 V at 0.24 ms, mean R-wave amplitude 15.3 mV and mean impedance was 627 Ω. Based on these values, device longevity was estimated at 12.5 years, with 94% lasting over 10 years. The efficacy of the device was further highlighted by the inclusion, approved by the US Food and Drug Administration (FDA), of pacemaker-dependant patients after analysis of the first 25 patients [19].

In terms of safety endpoints, the overall rate of major procedure- or system-related adverse effects at 6 months was 3.45%, corresponding to 28 complications in 25 patients, 4 of whom had unsuccessful implants. Traumatic cardiac injury was reported in 11 cases (1.5%) with 3 cardiac perforations (0.41%) and 8 pericardial effusions (1.1%), higher than usually reported in transvenous pacemaker implantations. Other complications included 5 access site complications (0.69%), 2 thromboembolic events (0.28%), 2 pacing issues (elevated thresholds, 0.28%) and 8 other complications (1.1%). Compared with a historical cohort of 2667 transvenous implants, and after adjustment for differences in population, the Micra patients had a lower risk of major complications (hazard ratio 0.46, confidence interval 0.28–0.74, p = 0.006), although these *post-hoc* results must be interpreted with caution. Concerning the risk of cardiac perforation specifically, mechanical assessment of the Micra™ delivery system in cadavers pointed to an acceptable margin between the force exerted at the tip of the catheter and the force necessary to perforate the RV [20], although these are not clinical data and perforation of other structures (vena cava, right atrium, etc.) has not been evaluated. The possibility of mechanical trauma linked to the delivery system is also highlighted by the presence of transient atrioventricular block or right bundle-branch block in some

patients. Overall, however, the implant procedure was well tolerated in the Micra TPS study, with a mean time to discharge of 1 day in the analysis of the first 140 patients [17].

The system has been available for limited market release in Switzerland since June 2015.

Nanostim™ Leadless Cardiac Pacemaker

The LEADLESS study [14] was a multicentre, single-arm European study evaluating the safety and efficacy of the Nanostim™ LCP device in 33 patients. Similarly to the Micra TPS study, patients were included if they had an indication for single-chamber pacing, consisting of: (1) permanent atrial fibrillation with atrioventricular block or slow ventricular response; (2) normal sinus rhythm with second- or third-degree atrioventricular block and a low level of physical activity or short expected life span; or (3) sinus bradycardia with infrequent pauses or unexplained syncope with electrophysiological findings. The initial results have been described in previous reviews [21, 22], and showed a 97% rate of successful implantation, 70% requiring only one deployment of the device, and two serious adverse device endpoints (one tamponade and one placement in the left ventricle via a patent foramen ovale). Retrospective 1 year analysis of the LEADLESS trial [23] showed an absence of further complications and stable pacemaker performance values (mean pacing threshold at a 0.4 ms pulse width of 0.43 ± 0.30 V; R-wave amplitude of 10.3 ± 2.2 mV; and impedance 627 ± 209 Ω). More recently, interim results of the LEADLESS II study, a prospective, nonrandomised, multicentre study aimed at obtaining FDA approval for the Nanostim™ device, have been published [24]. The primary analysis concerned the 6-month safety and efficacy results of the first 300 patients, but the study also published the outcomes of all 526 patients enrolled to date. Inclusion and exclusion criteria were similar for the LEADLESS trial, although pacemaker-dependant patients were no longer excluded. The results showed a Nanostim™ implantation success rate of 95.8%, with a mean procedure time of 28.6 ± 17.8 minutes, and fluoroscopy time of 13.9 ± 9.1 minutes, once again significantly longer than for a transvenous VVI pacemaker. Similarly to the LEADLESS trial, 70.2% of devices were successfully implanted after initial deployment. Mean hospital stay was comparable to that in the Micra TPS study (1.1 ± 1.7 days). Regarding pacemaker efficacy at 6 months, 90% of patients reached the combined primary efficacy endpoint of (1) acceptable pacing threshold (≤2.0 V at 0.4 msec) and (2) an acceptable sensing amplitude (R wave ≥5.0 mV, or a value equal to or greater than the value at implantation). In the total cohort, the mean values at 12 months were: R-wave amplitude 9.2 ± 2.9 mV and pacing capture threshold (at 0.4 msec) 0.58 ± 0.31 V. According to results at the 6-month follow-up, battery longevity could be estimated to be 15 ± 6.7 years.

With regards to safety, the rate of device-related serious adverse events was 6.7% over 6 months, with 1.3% cardiac perforation, 1.7% device dislodgement, 1.3% elevated pacing thresholds necessitating device retrieval and replacement, and 1.3% vascular complications. This study also pointed to a learning curve, as in most medical procedures, with an almost halved rate of complications after 10 procedures (3.6 vs 6.8%), although this difference was not statistically significant. Of note, another long-term safety trial is ongoing in Europe (The LEADLESS Observational Study; NCT02051972).

Wireless cardiac resynchronisation therapy system

Initial evaluation of the WiCS™ device was performed in the WISE-CRT study [15], which was a multicentre European prospective observational study evaluating the feasibility and safety of the system. It aimed to enrol 100 patients with indications for CRT therapy and with either failed coronary sinus lead implantation, clinical nonresponse after conventional CRT implantation or necessity to upgrade to a CRT system. The study was interrupted prematurely after just 17 patient enrolments, because of a high rate (three patients or 18%) of procedural serious pericardial effusions linked to manipulation of the delivery catheter or guidewire, with one fatality. Of the 17 patients, 1 additional subject had a failed implantation as a result of inadequate pacing thresholds. From an efficacy point of view, the system showed promising results in the few patients followed-up for 6 months.

Following revision of the delivery system, the WiCS system is currently under evaluation in the SELECT-LV nonrandomised trial [25]. Early results from 35 patients continue to show promising results in terms of efficacy, with a shortening in mean QRS duration from 174 to 137 ms at 1 month, an improvement of LV ejection fraction from 27 to 33.7% at 6 months and reduced ventricular volumes. Importantly, patients also showed an improvement in their New York Heart Association (NYHA) class from 2.6 to 1.8 at 6 months. With regards to safety, there were no cases of tamponade with the revised delivery system. Nevertheless, rates of complications were not negligible, with 4 of the 35 patients suffering device- or procedure-related events within 24 hours (one groin fistula necessitating surgery, one groin pseudoaneurysm treated conservatively, one

electrode embolisation to the lower leg and one case of ventricular fibrillation with aborted implantation). At 1 month, there were 10 further complications, 7 related to the device and 3 concerning infection.

Remaining questions

Leadless right ventricular pacing

To date, no data exist regarding the actual battery longevity of leadless pacemakers, the only indications coming from theoretical calculations or estimates based on early results of the aforementioned studies. Moreover, much of the data was retrieved from non-pacemaker-dependant patents, such as in the LEAD-LESS trial. Even in the LEADLESS II trial, mean rates of ventricular pacing were 51.6% at 12 months. Nevertheless, these estimates point toward similar device longevity to single chamber conventional pacemakers. In the case of the Nanostim™, the high efficiency of the unit results in a current drain of approximately 1 µA, around six times less than a transvenous unit from the same manufacturer [22]. As illustrated in table 1, the projected device longevity of the Micra™ at the International Organization for Standardization (ISO) values is substantially less than the Nanostim™, but thanks to energy-saving algorithms such as capture management, the projected values at real-world settings are improved.

Furthermore, the optimal strategy once a leadless device reaches the end of its service is unknown. Device abandonment with placement of a new device has yet to be tested comprehensively. Removal of a chronically implanted leadless pacemaker also remains poorly studied in humans, the only data emanating from the LEADLESS II study where seven patients underwent successful retrieval of devices that had been implanted 160 ± 180 days previously. In the Micra TPS study, one patient underwent successful percutaneous removal 17 days after implantation because of intermittent loss of capture. Even available animal data concern relatively recently implanted devices (5 months in 10 sheep implanted with a Nanostim™ [26] and 18 months in 4 sheep implanted with a Micra™ [27]). Moreover, the optimal strategy in the event of infection of the leadless pacemaker remains unclear. Data from the LEAD-LESS II study showed an uncomplicated percutaneous retrieval of six embolised devices (four in the pulmonary artery and two in the right femoral vein) relatively early after implantation (8.0 ± 6.4 days).

The effectiveness of the rate-response algorithms in leadless pacemakers has yet to be studied. In the case of the Micra TPS study, no treadmill data are available yet. For the Nanostim™ device, 1-year retrospective analysis of the LEADLESS trial described an adequate rate-response function in the 19 patients out of 31 programmed in VVIR at 12 months. Evaluation of rate response will be interesting to follow, especially in the case of the Nanostim™, as the responsiveness of central venous temperature to an increase in activity may be slower than the more standard accelerometer used in the Micra™. The performance of the novel rate-response algorithm used by the Micra™ also needs to be evaluated.

Although both devices are labelled "MRI conditional" because of the lack of ferrous components, currently data are lacking. One case of a Micra™-implanted patient safely undergoing a 1.5 Tesla (T) magnetic resonance imaging (MRI) scan of the brain was reported in the Micra TPS study [17]. Theoretical data based on modelling results predict a reduced risk of MRI interaction with the Micra™ device compared with conventional devices, with a predicted rise in temperature of less than 0.4° in 99% of cases at 1.5 T and 3 T [28]. More clinical experience is needed before the devices can be considered fully MRI safe.

Leadless endocardial left ventricular pacing

The efficacy results of the Wise-CRT and SELECT-LV trials seem to indicate the systems could be a useful alternative to standard CRT systems in cases of nonresponse or LV lead failure, but data are available for only a short follow-up of 6 months. Obviously the main concern with the system remains the safety of the implantation procedure, which is not fully addressed, as well as the currently unknown rate of chronic complications.

Other concerns are the seemingly short battery life of the device; in the Wise-CRT study, projected battery longevity after 6 months follow-up was only 18 months (range 9–42 months). Ease of extraction and/or replacement of the different devices contained in the system remains unknown. Issues with restricted acoustic windows that limit energy transmission need to be addressed. Finally, the thromboembolic risk linked to the leadless receiver unit in the LV in comparison with standard transvenous LV leads needs to be further studied.

Future directions

One important issue that will be addressed in the future is the possibility of multichamber leadless pacing, although anchoring the device in a safe and effective manner in the thin-walled atrium, and issues with additional energy requirements resulting with communication between the devices, need to be addressed. Currently the available RV pacing devices only allow

single-chamber ventricular pacing, thus restricting their application in everyday life, with rates of VVI pacemaker implantation at around 8–25% according to different regions of the world [6, 29]. The combination of leadless devices with the subcutaneous defibrillator (Boston Scientific, Marlborough, MA, USA) will allow antitachycardia and antibradycardia pacing, and will be introduced in the near future. Finally, researchers are working on a device which will harvest kinetic energy from the heart's motion for providing power – thereby dispensing of the need for device replacement.

Conclusions

Leadless pacemakers are a milestone in pacing therapy. They are clearly the preferred pacing modality in a niche group of patients (e.g., those with venous access issues), but they can be considered in other situations where VVI(R) pacing is indicated. Currently, only one system is commercially available in Switzerland, with a limited market release. The implantation procedure requires special skills that need to be acquired properly, as complications such as tamponade are a concern. Other issues are management at battery depletion, extractability, and cost (which is likely to evolve depending upon the uptake of the technology and the introduction of new models from competitors). The therapy will no doubt continue to evolve, and provide us with more treatment options for our patients.

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