

The wireless pacemaker is on again; from electro-stimulation to synchronization

Filippo Stazi*

UOC Cardiologia d'Urgenza, Ospedale San Giovanni Addolorata, Roma

KEYWORDS

Wireless pacemaker;
Resynchronization therapy;
Cardiac pacing (electro-stimulation)

Leadless stimulation of the right ventricle is now a reality, especially in patients with very specific indications and clinical characteristics, even in the absence of randomized studies to support its use. The reduction of device costs and the refinement of atrioventricular synchronization algorithms will sanction its greater diffusion in the future. The possibility of using leadless technology also for resynchronization therapy, on the other hand, is currently a promising option but, pending randomized studies with robust case histories and adequate follow-ups, it should still be considered as a niche therapy, to be limited to centres highly specialized and in patients in whom conventional resynchronization has been impossible or ineffective.

The introduction of transvenous cardiac pacing (electro-stimulation) in the middle of the last century marked one of the main advances in modern medicine, allowing an improvement in the quality of life and, in many cases, a reduction in mortality of patients suffering from bradyarrhythmias. Over the years, the technology has evolved significantly, allowing the implantation of devices for the prevention of sudden death (defibrillators) and the treatment of heart failure [resynchronization, cardiac resynchronization therapy (CRT)], but nevertheless, this therapy is still associated with a significant risk of complications, basically linked to the presence of the leads and the pocket in which the device is housed. Short-term complications range from 9.5% to 12.6% and are mainly caused by electrode dislocation and, less frequently, by pocket haematoma, pneumothorax, or cardiac tamponade. Long-term complications account for an additional 9% and are caused by lead malfunction, endocarditis, venous obstruction, severe tricuspid insufficiency, pocket problems (infection and skin erosion), often require reoperation, and are possible causes of increased morbidity and mortality. The only possible solution to these problems is in the elimination of the two main sources of complications: the leads and the pocket. For this purpose, the so-called wireless pacemakers have been developed. The first (Nanostim)

received the CE mark in 2013 and is awaiting approval by the FDA, the second (MICRA) was approved by the European Commission in 2015 and by the FDA the following year.

The present

Both devices are implanted in the wall of the right ventricle which they reach, through a catheter, via the femoral vein and the inferior cava. The Nanostim is fixed through a screw mechanism, the Micra through four teeth. Both the Nanostim and the Micra weigh 2 g but the former is longer (41.4 mm) and narrow and can therefore be implanted with an 18-Fr sheath, while the latter is shorter (25.9 mm) but wider and requires a 23-Fr sheath. Both are magnetic resonance imaging conditional, the Nanostim at 1.5 Tesla, the Micra also at 3 Tesla. Both devices have the rate responsive function. The expected longevity at nominal stimulation parameters is 15 years for the Nanostim and 12.5 for the Micra. At the moment, given the limited number of years that have passed since the first implants, it is not possible to be certain of these estimates. The Nanostim interacts with the manufacturer's programmer and shows the endocavitary electrogram, the status of the device, and can be programmed. The Micra interacts with the manufacturer's programmer, has the self-capture algorithm and provides

*Corresponding author. Email: filippostazi67@gmail.com

data on the percentage of stimulation, evolution of the sensing amplitude, threshold, and stimulation impedance.

The data available

Nanostim was evaluated in the LEADLESS,¹ LEADLESS II,² and LEADLESS Observational Study³ studies. The Micra in the Micra Transcatheter Pacing Study⁴ and in the Micra Transcatheter Pacing System Post-Approval Registry,⁵ for a total of ~1500 patients. For both devices, implant success occurs in 95-99% of cases. The freedom from complications is 94% for the nanostim and 96-98.5% for the Micra. At greater risk of procedural complications, especially perforation, are the elderly, frail women, subjects with low body mass index, patients on chronic steroid therapy, those who have undergone multiple electrode repositioning in an attempt to find the best position and those with (where) the device (is) implanted apically. The screw mechanism of the Nanostim seems to increase both the risk of perforation and dislocation: an excessive penetration of the screw, in fact, increases the risk of perforation while a penetration defect increases the possibility of dislocation. Both of these events, however, decrease in parallel with the improvement of the experience of the operators. The most frequent complications, in addition to the aforementioned perforation, are of the vascular type at the entrance to the system (haematoma, pain, pseudoaneurysm, and arteriovenous fistula). There are no direct comparisons between the two devices, but the implant complication rates and the 6-month performance seem similar, apart from the acute dislocation of the device, which has so far only been reported with Nanostim (1.1% in LEADLESS II). The electrical measurements of sensing, capture, and impedance are usually good and tend to remain stable over time, like what happens with transvenous pacemakers. The (system) threshold value at the implant is important as it predicts its subsequent evolution. With Micra, e.g. it is necessary to obtain threshold values $<2\text{V}/0.24\text{ms}$.⁶

In 2016, problems related to the Nanostim battery emerged, involving 2.4% of all devices implanted up to that time. These defects caused the affected devices to have a longevity of <2 years. In 2017, following another defect in the device related to explantation procedures, the Nanostim was removed from the market and at the moment, therefore, the Micra is the only leadless pacemaker available.

Comparison with traditional pacemakers

There are no randomized comparisons between leadless pacemakers and transvenous devices. In the absence of these, comparisons with historical groups were conducted. In the MICRA TPS Trial,⁷ the leadless device was compared with a historical control group of 2667 patients implanted with both single and dual-chamber transvenous pacemakers. The major complication rate was 4.0% in the Micra group and 7.6% in the control group (hazard ratio 0.52, 95% confidence interval 0.35-0.77; $P=0.001$). This reduction was associated with a 47% drop in the extension of hospitalization and 82% in revisions of the device. The greatest advantage with leadless is in the reduction of late complications (>3 months after implantation). The rate of

cardiac perforations/pericardial effusion, on the other hand, is higher in leadless pacemakers. A meta-analysis⁸ of 28 studies, including 60 744 conventionally implanted subjects, in fact showed an incidence of perforations of 0.82% against 1.6% of the studies with the new devices. The risk of infection with leadless is certainly lower than with traditional devices and, in addition, it seems manageable with antibiotic therapy, without the removal (having to resort to explanting) of the device.

The duration of the leadless implant procedure is generally shorter and functional recovery is faster. The absence of the wound also entails undoubted aesthetic advantages, as well as the ability to resume driving vehicles early. Also allowed are those activities (such as golf or hunting) that traditional pacemakers make difficult.

The indications

In consideration of the device's ability to stimulate only the ventricular chamber, the main indication lies in atrial fibrillation with low ventricular response. The leadless pacemaker can however also be considered in the case of paroxysmal AV blocks, sinus node disease or syncope, in which a high percentage of pacing is not expected. Other cases in which leadless may be the best choice are patients at high risk of systemic infection or who have already experienced an infection from an implantable cardiac device. Furthermore, leadless pacing is the only possibility (except epicardial access with its inherent difficulties in obtaining low and stable thresholds) when the upper central venous system is damaged, as in the case of previous transvenous pacemaker implantation, catheter permanent infection, thoracic surgery, radiotherapy for thoracic tumours, or trauma. The new devices should then be strongly considered in the case of dialysis, both to save the venous access necessary for fistulas, and because the increased rate of transient bacteraemia during dialysis can lead to haematogenous infection of the leads. Leadless pacemakers, on the other hand, are less prone to such infections, probably due to their small size and being encapsulated within the heart wall.

Battery depletion and removal

The data relating to the extraction of chronically implanted devices are limited and absent for devices implanted for more than 3 years and largely come from the experience gained with the Nanostim, which suffered from premature battery depletion. However, the procedure seems safe and feasible, regardless of the duration of the implant and the type of device used. The success rate of the manoeuvre seems slightly higher with the Micra and tends to decrease as the temporal distance from the implant increases. A comparison between the two devices is not correct given the significant differences in time to the extraction of the studies reported in the literature, but it is possible that the different electrode fixing mechanism makes it easier to remove the Micra. No cardiac perforations have been reported with either device. In case of failure to remove it is always possible to reprogramme the devices in OOO mode and leave them inside the ventricular wall, implanting a new one in a different position. In fact,

it is estimated that, given the small size of the devices, corresponding to <2% of its normal volume, the right ventricle can host up to three without negative consequences. Which, with the expected longevity of about 15 years per device, should ensure coverage for the entire life expectancy for those subjected to the implantation of such devices.

The future

VDD stimulation

To overcome the limitations imposed by VVI stimulation alone, the Micra has been enriched with a three-dimensional accelerometer capable of sensing the atrial contraction and consequently allowing VDD stimulation, that is, to synchronize ventricular pacing with atrial activity. The use of a dedicated downloadable algorithm has shown its effectiveness, both at rest and during walking, in the MARVEL study⁹ in which, in acute, atrioventricular synchrony increased from 37.5% of VVI pacing to 80% of that VDD. The subsequent MARVEL 2¹⁰ in 75 patients with persistent atrioventricular block confirmed an increase in atrioventricular synchrony, from 26.8% to 89.2%, moving from VVI 50 to VDD pacing. This percentage was reduced to 69.8% when the patients were standing upright. However, 95% of patients had $\geq 70\%$ coordination between the atrium and ventricle. Furthermore, no pauses or tachycardia induced by atrial over-sensing were observed. However, it should be borne in mind that the system does not allow to maintain synchronism for heart rates >105 b.p.m. and therefore is not currently the optimal choice in young or otherwise physically active subjects. In addition, the algorithm, due to its high energy consumption, is currently only downloadable, for temporary use and not physically incorporated into the device. A clinical case¹¹ has recently been published in which the Micra implanted in the right ventricle was synchronized with a transvenous pacemaker positioned in the right atrium.

Leadless DDD stimulation

A dual-chamber stimulation (atrium and ventricle) requires the presence of two devices, one implanted in the atrial wall and the other in the ventricular one, which are capable of communicating with each other in real time, through the emission and reception of signals. In order to ensure a suitable longevity of the battery, this communication must require a minimum energy consumption. Bereuter¹² has experimented in animals with a prototype of this kind in which blood and myocardium are the means of transmission of electrical signals. Each of the two devices emits small alternating current signals, which are transmitted to the tissues through which they propagate and are detected almost simultaneously by the other device, so as to provide synchronized atrioventricular stimulation. The power consumption seems modest, $\sim 0.1\%$ of the total consumption, and therefore not such as to significantly reduce the battery life. Signal transmission did not induce arrhythmias or tissue overheating. The system must obviously be tested in

humans before further comments can be made on the matter. Among other things, the fears related to the risk of perforation of a thin wall such as that of the atrium during the implantation procedure still remain to be dispelled.

Leadless pacemaker and subcutaneous defibrillator

In some clinical cases, the possibility of the combined use of a leadless pacemaker and a subcutaneous defibrillator has been demonstrated.¹³ In particular, the pacing of the stimulation system is correctly interpreted by the defibrillator, the simultaneous communication of the two devices with their respective programmers does not interfere with their correct functioning; the communication between the leadless pacemaker and its programmer does not induce over-sensing phenomena in the subcutaneous defibrillator and, finally, the shock delivered by the defibrillator did not change the position and function of the leadless device.

Leadless CRT

Traditional CRT has a significant percentage of failure, both due to the inability to position the catheter intended for epicardial stimulation of the left ventricle and due to lack of response to stimulation. These negative aspects could be overcome by the use of endocardial stimulation of the left ventricle, which offers the advantages of a more physiological activation, from the endocardium to the epicardium, and therefore more effective, of greater freedom in the positioning of the electrode and of the absence of the stimulation of the phrenic nerve, one of the most frequent causes of transvenous CRT implant failure.

A wireless methodology of endocardial stimulation of the left ventricle using the Wireless Stimulation Endocardially for CRT (WISE-CRT) system is currently undergoing advanced experimentation. This system provides wireless stimulation by transmitting acoustic energy from a pulse generator transmitter, implanted under the skin, to a receiver electrode, implanted in the left ventricular wall. This converts acoustic energy into electrical energy and uses it for pacing. The pulse generator consists of a battery and transmitter connected together by cable. The WISE(R)-CRT system can be implanted with any device capable of stimulating the right ventricle. The biventricular stimulation is obtained through the sensing of the signal produced by the pacing of the right ventricle operated by the co-implanted device. This signal is used as a trigger for left ventricular pacing. The implantation of the WISE-CRT is in two successive steps: in the first, the generator is surgically implanted in an intercostal space, generally between the fourth and sixth rib, along the parasternal line; in the second, the wireless electrode is implanted in the wall of the left ventricle, where it is fixed with a barbed anchoring system, by retrograde trans-aortic route or, alternatively, by a trans-septal approach.

The feasibility and safety of the device were evaluated in the WISE-CRT Study¹⁴ which enrolled 17 patients. In seven of these coronary sinus cannulation had previously failed, two had not benefited from a conventional CRT and, finally, eight were candidates for upgrade, as they already

had a pacemaker or defibrillator. The procedure was successful in 13 of the 17 subjects (76%) and at 6 months all 13 patients who had been implanted were alive, although 7 major adverse events occurred in 6 patients (35%). At 6 months, as far as system performance was concerned, ventricular pacing was detected in 92% of subjects. In addition, two-thirds of the patients presented an improvement in at least one functional class and a significant increase of at least six points in the ejection fraction of the left ventricle. However, due to a high (18%) incidence of peri-procedural cardiac tamponade, the study was prematurely interrupted after the first 17 enrolments. A next generation device was therefore developed, with the addition of a balloon on the tip of the catheter used for the implantation of the left ventricular electrode, aimed at inducing less trauma to the ventricular wall. The new system was tested in the Safety and performance of Electrodes implanted in the Left Ventricle study.¹⁵ Total 35 of the 39 enrolled patients underwent the procedure, which was successful in 34 (94.4%). There was no cardiac tamponade. After 6 months, biventricular pacing was achieved in 93.9% of patients and 84.8% had shown clinical improvement. During this follow-up period, a hematoma of the pocket, two cases of infection of the subcutaneous device were observed and the device was removed in one patient. The first randomized study is currently underway, the Stimulation Of the left Ventricular Endocardium for C(ardiac) Resynchronization Therapy in Non-Responders and previously Untreatable Patients Study¹⁶ aimed at evaluating the safety and efficacy of the system in a cohort of 350 patients, who after implantation will be randomized to ON or OFF stimulation, in order to evaluate both symptomatic and echocardiographic effects of the method. The WISE-CRT has proven to be compatible with both conventional right ventricular pacing devices and the Micra,¹⁷ and can therefore enable true leadless resynchronization therapy. In one case,¹⁸ the subcutaneous defibrillator was also associated.

The WISE-CRT is an interesting device full of potential but, at the moment, still held back by important limitations. First of all, to obtain optimal stimulation of the left ventricle, the transmitter must be able to concentrate the acoustic energy produced on the receiving electrode. A severe angle between the two system components, a distance between them >10cm or the absence of a good acoustic window (occurring in about 10% of patients) between the two devices therefore reduces the efficiency of the system. Furthermore, in subjects with marked ventricular dilatation, it may be difficult to position the electrode in some segments of the lateral wall of the ventricle, as delivery sheath currently involves only one type of curve. Another aspect to consider is the possible risk of thromboembolic events following implantation in the left ventricular wall of the electrode. Since the complication rate, even serious, is not negligible, for the moment the procedure is to be limited to centres with greater expertise and always making use of the cardiac surgery stand-by. Another aspect that requires technological improvement is the inability of the device to determine the percentage of actual biventricular stimulation. Finally, it is necessary to consider the

possibility of battery depletion at different times, with the consequent need for multiple replacement interventions.

Conclusion

Leadless stimulation of the right ventricle is now a reality, especially in patients with very specific indications and clinical characteristics, even in the absence of randomized studies to support its use. The reduction of device costs and the refinement of atrioventricular synchronization algorithms will sanction its greater diffusion in the future.

The possibility of using leadless technology also for resynchronization therapy, on the other hand, is currently a promising option but, pending randomized studies with robust case histories and adequate follow-ups, it should still be considered as a niche therapy, to be limited to centres highly specialized and in patients in whom conventional resynchronization has been impossible or ineffective.

Conflict of interest: none declared.

References

- Reddy VY, Knops RE, Sperzel J, Miller MA, Petru J, Simon J, Sediva L, de Groot JR, Tjong FVY, Jacobson P, Ostroff A, Dukkipati SR, Koruth JS, Wilde AAM, Kautzner J, Neuzil P. Permanent leadless cardiac pacing results of the LEADLESS trial. *Circulation* 2014;**129**:1466-1471.
- Reddy VY, Exner DV, Cantillon DJ, Doshi R, Bunch TJ, Tomassoni GF, Friedman PA, Estes NAM, Ip J, Niazi I, Plunkitt K, Banker R, Porterfield J, Ip JE, Dukkipati SR. Percutaneous implantation of an entirely intracardiac leadless pacemaker. *N Engl J Med* 2015;**373**:1125-1135.
- Sperzel J, Defaye P, Delnoy P-P, Garcia Guerrero JJ, Knops RE, Tondo C, Deharo J-C, Wong T, Neuzil P. Primary safety results from the LEADLESS Observational Study. *Europace* 2018;**20**:1491-1497.
- 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, Bongiorno MG, Knops RE, Ellis CR, Gornick CC, Bernabei MA, Laager V, Stromberg K, Williams ER, Hudnall JH, Ritter P. A leadless intracardiac transcatheter pacing system. *N Engl J Med* 2016;**374**:533-541.
- Roberts PR, Clementy N, Al Samadi F, Garweg C, Martinez-Sande JL, Iacopino S, Johansen JB, Vinolas Prat X, Kowal RC, Klug D, Mont L, Steffel J, Li S, Van Osch D, El-Chami MF. A leadless pacemaker in the real-world setting: the Micra Transcatheter Pacing System Post-Approval Registry. *Heart Rhythm* 2017;**14**:1375-1379.
- Piccini JP, Stromberg K, Jackson KP, Laager V, Duray GZ, El-Chami M, Ellis CR, Hummel J, Jones DR, Kowal RC, Narasimhan C, Omar R, Ritter P, Roberts PR, Soejima K, Zhang S, Reynolds D. Long-term outcomes in leadless Micra transcatheter pacemakers with elevated thresholds at implantation: results from the Micra Transcatheter Pacing System Global Clinical Trial. *Heart Rhythm* 2017;**14**:685-691.
- Duray GZ, Ritter P, El-Chami M, Narasimhan C, Omar R, Tolosana JM, Zhang S, Soejima K, Steinwender C, Rapallini L, Cicic A, Fagan DH, Liu S, Reynolds D. Long-term performance of a transcatheter pacing system: 12-month results from the Micra transcatheter Pacing Study. *Heart Rhythm* 2017;**14**:702-709.
- Vamos M, Erath JW, Benz AP, Bari Z, Duray GZ, Hohnloser SH. Incidence of cardiac perforation with conventional and with leadless pacemaker systems: a systematic review and meta-analysis. *J Cardiovasc Electrophysiol* 2017;**28**:336-346.
- Garweg C, Splett V, Sheldon TJ, Chinitz L, Ritter P, Steinwender C, Lemme F, Willems R. Behavior of leadless Av synchronous pacing during atrial arrhythmias and stability of the atrial signals over time. Results of the MARVEL evolve subanalysis. *Pacing Clin Electrophysiol* 2019;**42**:381-387.
- Steinwender C, Khelae SK, Garweg C, Chan JYS, Ritter P, Johansen JB, Sagi V, Epstein LM, Piccini JP, Pascual M, Mont L, Sheldon T,

- Splett V, Stromberg K, Wood N, Chinitz L. Atrioventricular synchronous pacing using a leadless ventricular pacemaker. Results from the MARVEL 2 study. *J Am Coll Cardiol EP* 2020;**6**:94-106.
11. Siroky GP, Bisht D, Huynh H, Mohammad A, Mehta D, Lam P. Synchronization of the new leadless transcatheter pacing system with a transvenous atrial pacemaker: a case report. *HeartRhythm Case Rep* 2020;**6**:899-902.
 12. Bereuter L, Gysin M, Kueffer T, Kucera M, Niederhauser T, Fuhrer J, Heinisch P, Zurbuchen A, Obrist D, Tanner H, Haeblerlin A. Leadless dual-chamber pacing. A novel communication method for wireless pacemaker synchronization. *J Am Coll Cardiol Basic Transl Sci* 2018;**3**:813-823.
 13. Tjong FVY, Brouwer TF, Smeding L, Kooiman KM, de Groot JR, Ligon D, Sanghera R, Schalij MJ, Wilde AAM, Knops RE. Combined leadless pacemaker and subcutaneous implantable defibrillator therapy: feasibility, safety and performance. *Europace* 2016;**18**:1740-1747.
 14. Auricchio A, Delnoy P-P, Butter C, Brachmann J, Van Erven L, Spitzer S, Moccetti T, Seifert M, Markou T, Laszo K, Regoli F, Ramos MA, Pasotti E, Scopigni F, Ramos MA, Hagne C, Siclari F, Demertzis S, Sinha A, Schalji M, Wellens HJJ, Padeletti L, Van Hemel N; for the 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. Reddy VY, Miller MA, Neuzil P, Søgaard P, Butter C, Seifert M, Delnoy PP, van Erven L, Schalji M, Boersma LVA, Riahi S. Cardiac resynchronization therapy with wireless left ventricular endocardial pacing: the SELECT-LV Study. *J Am Coll Cardiol* 2017;**69**:2119-2129.
 16. Singh JP, Abraham WT, Auricchio A, Delnoy PP, Gold M, Reddy VY, Sanders P, Lindenfeld J, Rinaldi CA. Design and rationale for the Stimulation Of the Left Ventricular Endocardium for Cardiac Resynchronization Therapy in non-responders and previously untreatable patients (SOLVE-CRT) trial. *Am Heart J* 2019;**217**:13-22.
 17. Carabelli A, Jabeur M, Jacon P, Rinaldi CA, Leclercq C, Rovaris G, Arnold M, Venier S, Neuzil P, Defaye P. European experience with a first totally leadless cardiac resynchronization therapy pacemaker system. *Europace* 2021;**23**:740-747.
 18. Sidhu BS, Gould J, Porter B, Elliott M, Mehta V, Niederer S, Rinaldi CA. Completely leadless cardiac resynchronization defibrillator system. *JACC Clin Electrophysiol* 2020;**6**:588-589.