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Review

Leadless pacemaker technology: clinical evidence of new paradigm of pacing

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Abstract

Despite continuous technological developments, transvenous pacemakers (PM) are still associated with significant immediate and long-term complications, mostly lead or pocket-related. Recent technological advances brought to the introduction in clinical practice of leadless PM for selected cohort of patients. These miniaturize devices are implanted through the femoral vein and advanced to the right ventricle, without leaving leads in place. Lack of upper extremity vascular access and/or high infective risk in patients requiring VVI pacing are the most common indications to leadless PM. The recently introduced MICRA AV leadless PM also allows ventricular synchronization through mechanical sensing of atrial contraction waves, thus solving the problem of AV synchronization. This review will discuss and summarize available clinical evidence on leadless PM, their performance compared to transvenous devices, current applications and future perspectives.

Keywords: Leadless pacing; Transvenous pacing; Nanostim; MICRA

1. Introduction

Transvenous pacemakers (PM) are well-known devices for the treatment of bradyarrhythmias, providing over one million people worldwide every year with life-saving pacing [1].

However, despite continuous technological developments, transvenous PM are still associated with significant complications, mostly lead or pocket related. Immediate and short-term complication rates can be as high as 12%. These short-term complications are mainly represented by pocket hematoma, pneumothorax, cardiac tamponade lead dislodgement [2,3]. In a study from Wiegand *et al*. [4] the corrected complication hazard of a DDD PM implantation was increased by 3.9 (1.4–11.3) compared to VVI and increased by 2.3 (1.1–4.5) compared to VDD pacing, mainly due to atrial lead dislodgement. The incidence of long-term complications such as tricuspid regurgitation, venous obstruction, lead fractures, insulation failure and device related infection is around 9% [3]; notably, transvenous lead-related endocarditis has been linked to higher mortality risk ranging from 12% to 31% [5]. In a Danish Cohort of patients followed from 1982 to 2018, overall risk of infection was low in PM implantations but considerably higher in Cardiac Resynchronization Therapy (CRT) systems and after reinterventions [6]. The FOLLOW-PACE multicentre cohort study aimed to identify patients more prone to complications and possible predisposing factors, but it still remains challenging to recognize high risk individuals [3]. The idea of solving this issues through a leadless and completely intracardiac pacemaker goes back to the 1970s [7], but it was only thanks to recent advances that leadless pacing became a clinical reality. This review will discuss and summarize available clinical evidence on leadless pacemakers, their performance compared to transvenous devices, current indications and future perspectives.

2. Implantation technique

Both existing systems, Nanostim leadless cardiac pacemaker (LCP) (St. Jude Medical/Abbott Laboratories, Chicago, IL, USA) and Micra transcatheter pacing system (TPS) (Medtronic, Minneapolis, MN, USA), are implanted with similar technique in the catheterization laboratory under fluoroscopic guidance. Each device is mounted on its own dedicated introducer sheath (Fig. 1) and is advanced to the right ventricle (RV) percutaneously through the femoral vein. Once in the RV, contrast medium is injected through the sheath to help localize the best implant site. The main objective is to avoid the ventricular free wall where the risk of perforation is higher while targeting the apex or, whenever technically feasible, a septal position that has shown similar electrical performance [8]. Fixation is achieved by either a screw-in helix (Nanostim LCP) or successful attachment of at least 2 of 4 nitinol tines (Micra TPS). After electrical performance testing and confirmation of stability with a tug test, the device is released from the delivery system. Antibiotic prophylaxis and peri-procedural haemostasis are left at operator decision and centre-specific guidelines; evidence suggests that uninterrupted therapeutic anticoagulation represents a safe option associated with shorter in-hospital length of stay [9]. Flushing the introducer with heparinized saline solution, however, is recommended in

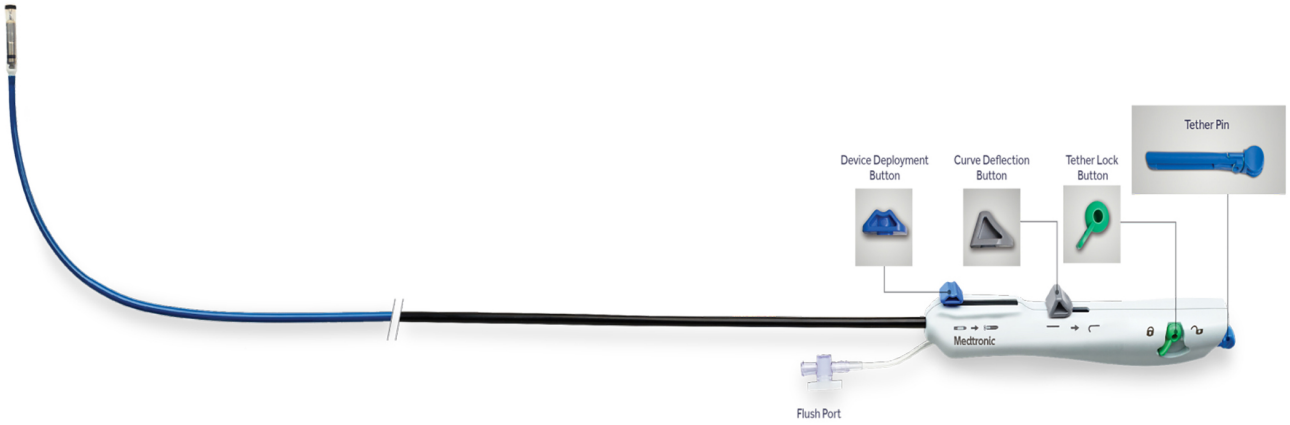

Fig. 1. Micra Integrated Delivery Catheter. 105 cm long catheter system with a handle that controls deflection and deployment of the Micra pacing capsule (23 Fr inner diameter/27 Fr outer diameter). Courtesy of Medtronic Inc.

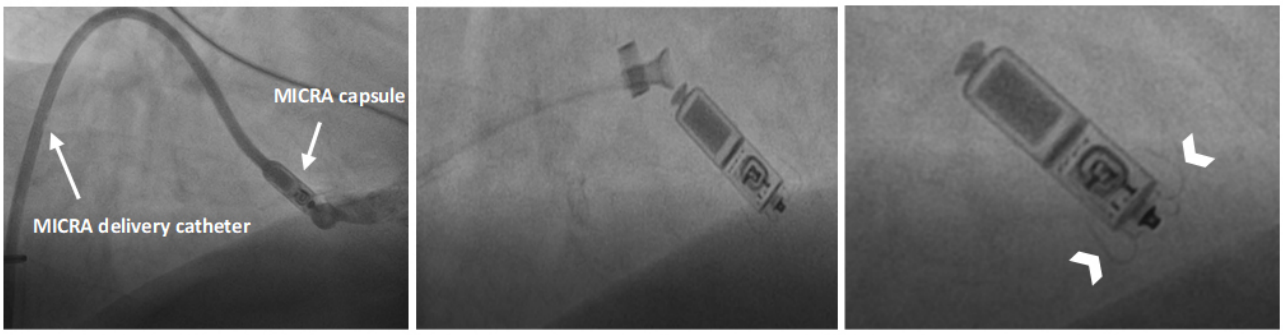

Fig. 2. MICRA deployment steps. Left panel: Delivery catheter is advanced to the right ventricle and contrast medium is injected to confirm appropriate positioning. Middle panel: MICRA capsule is released, and a tug test is performed to verify stability. Right panel: MICRA device in place (arrowheads show nitinol tines).

all patients [10,11]. Implantation technique steps are illustrated in Fig. 2.

3. Leadless systems

The Nanostim LCP (St. Jude Medical/Abbott Laboratories, Chicago, IL, USA) was the world's first available leadless PM. The Nanostim system received the Conformitè Europeenne (CE) mark in 2013, but it still awaits US Food and Drug Administration (FDA) approval after two major recalls due to issues regarding premature battery depletion and docking button detaching. The Micra TPS (Medtronic, Minneapolis, MN, USA) was CE approved in 2015 and subsequently, FDA approved in 2016. The subsequent Micra AV was designed as a single chamber PM able to ensure AV synchrony [12] and was FDA approved in 2020. The two devices share many similarities but differ in some relevant features (Fig. 3). Particularly, the Nanostim LCP measures 41.4 $\times$ 6 mm and has a volume of 1 cm^3, while the Micra TPS is 26 $\times$ 6.7 mm for a volume of 0.8 cm^3. They are both implanted in the RV through a percutaneous femoral approach and the introducer sheaths measure 18F/21F (inner diameter/outer diameter) for the Nanostim LCP and 23F/27F (inner diameter/outer diameter) for the Micra TPS. The Nanostim LCP uses an active fixation screw in helix while the Micra uses 4 flexible, electrically inactive nitinol tines to attach to the myocardium. For interrogation and programming purposes, the Nanostim LCP uses electrocardiogram (ECG) electrodes that allow signal transmission through 250 kHz pulses, thus reducing battery consumption, whereas the Micra TPS uses conventional radiofrequency currents. Rate responsiveness is achieved with a temperature-based sensor for Nanostim LCP and with a 3axis accelerometer for Micra TPS [13]. Approximate durability is 10 years for both devices. Currently, only the Nanostim LCP has a dedicated catheter for retrieval, but there are reports of successful Micra retrieval using the introducer sheath and gooseneck snares [14]. They are both conditionally safe for full body magnetic resonance imaging in 1.5 and 3.0 Tesla scanners.

4. Safety and efficacy data

4.1 Nanostim LCP

The first human trial on leadless pacing was the LEADLESS study, in which the Nanostim device was im-

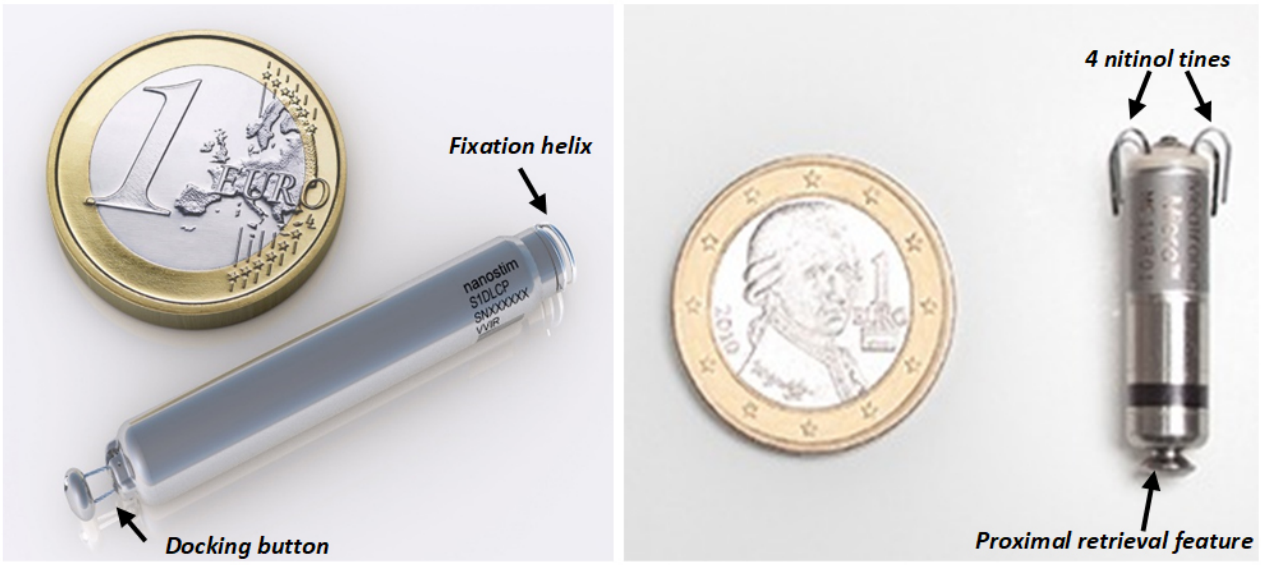

Fig. 3. Nanostim LCP (on the left) and Micra TPS (on the right) dimensions compared with a coin. Attchment and retrieval features are shown for both devices.

planted in 33 participants. The primary safety end point of freedom from complications was reached in 31 out of 33 subjects (94%), with only one serious adverse event described. It consisted of cardiac perforation and tamponade surgically managed but eventually led to the death of the patient on the 18th post-operative day [10]. After a follow-up of 3 months and then 1-year, electrical parameters were stable and there were no device-associated adverse events [10,15].

The subsequent prospective non-randomized LEADLESS II trial enrolled 527 subjects. The primary outcome analysis was a prespecified assessment of the primary efficacy and safety end points in the first 300 patients who were followed for 6 months (primary cohort). During a period of 6 months of follow-up, the primary efficacy endpoint consisted of a combination of adequate pacing thresholds and sensing amplitudes, while the primary safety endpoint was freedom from device-related serious adverse events. The efficacy end point was met in 270 of 300 subjects (90%) and the safety end point in 280 of 300 (93.3%). Twenty patients (6.7%) experienced an adverse event, including cardiac perforation (1.3%), device dislodgement (1.7%), elevated pacing thresholds requiring retrieval and replacement (1.3%), and vascular complications (1.3%) [16]. More recently, the LEADLESS Observational Study, a prospective, single-arm, multicentre, post-market study, was conducted to assess safety of the Nanostim in a real-world setting. The study was initially stopped after 131 implantations due to two separate events of cardiac perforation that led to patients' death. After protocol changes and adequate operator training, freedom from serious adverse events was observed in 94.6% (285 out of 300 patients) at 6 months of follow up. The most frequently reported complications were implantation-related, specifically cardiac perforation (1.3%, n = 4) and vascular complications (1.3%, n = 4) [17].

At present, a worldwide battery advisory was issued by the Nanostim manufacturer. Seven patients who had been implanted with the device had an unexpected battery failure that resulted in abrupt loss of pacing and communication; therefore, immediate replacement of the Nanostim with a traditional device was required in PM-dependent patients.

4.2 Micra TPS

The Micra investigational device exemption (IDE) study was a prospective multicentre trial that investigated the safety and efficacy of the Micra TPS in 725 patients with a class I or II guideline indication for VVI pacing, during a period of 6 months. The device was successfully implanted in 719 of 725 patients (99.2%). Complications were recorded in 4% of patients, including cardiac perforation (1.6%), vascular complications (0.7%) and venous thromboembolism (0.3%). Only one death occurred but it was not procedure-related, but due to metabolic acidosis and renal failure. No device dislodgements were reported. In this study, the primary efficacy endpoint of low and stable pacing capture threshold was reached in 98.3% of patients.

The Authors of IDE study also performed a post hoc analysis in which major complications rate was compared with major complications rate of propensity-matched control cohort of 2667 patients with transvenous PM: a 48% reduction in major complications in the MICRA group was observed [18].

The Micra TPS Post Approval Registry (PAR) was a prospective, nonrandomized, multicentre registry aiming to assess the safety and effectiveness of the Micra system in

a real-world setting. The study interim analysis of the first 795 patients at 30 days post implant was initially published. The inclusion criteria were the same as the previous Micra IDE study [18]. The device was successfully placed in 792 patients (99.6%). At 30 days 97.0% had a pacing capture threshold <2.0 V. A total of 13 serious adverse (1.5%) events in 12 patients occurred, of whom the most common were vascular complications (0.75%), followed by pacing issues (0.25%), deep vein thrombosis (0.13%) and cardiac perforation (0.13%). Notably, 5 patients (0.63%) developed pericardial effusion but only 1 (0.13%) met the criteria for serious adverse event. This lower rate of perforations has been linked by the Authors to the 52% rate of non-apical positioning of the device in the Micra PAR, as opposed to the 33% of the Micra IDE [18,19]. Twenty-two patients died during the Micra PAR study, but none of the deaths was attributable to the Micra system [19].

Subsequently, the results of 12-month follow-up of the Micra PAR on 1817 subjects were published too.

The Micra device was successfully implanted in 1801 of 1817 patients (99.1%). Adverse event rate was 2.7%, with the most common being vascular complications (0.6%) and cardiac perforation (0.4%). Safety data of patients of the Micra PAR study were also compared with patients from the Micra IDE study and with an historical cohort of 2667 patients with a conventional transvenous PM. The major complication rate trended lower in the Micra PAR than in the IDE study (hazard ratio 0.71; 95% Confidence Interval (CI) 0.44–1.1; $p = 0.160$) while there was a 63% lower risk of major complications in the Micra PAR compared to the historical cohort of transvenous PM (hazard ratio 0.37; 95% CI 0.27–0.52; $p = 0.001$). This was driven by significantly lower pericardial effusion rates in the Micra PAR (0.44% vs 1.52%; $p = 0.009$). The electrical performance met the efficacy end point of <2 V pacing threshold in 97% of patients [20].

5. Leadless vs transvenous pacemakers

At present, there are no randomized trials directly evaluating safety and performance of leadless PM with traditional devices and data are mainly derived from observational studies using historical cohorts of conventional PM. It must be kept in mind, however, that these results may be influenced by underreporting of complications of transvenous PM and by the novel technology represented by leadless system; with particular regard to this, periprocedural complications rate can be related to operator experience, especially during the learning curve. This is clear, for example, looking at complications rate reported in Micra PAR vs Micra IDE study [18,19]; in the former, the lower rate of cardiac perforations probably reflects the operator learning curve together and a preferential non-apical positioning of the Micra TPS [18,20].

Recently, the results of the Longitudinal Coverage with Evidence Development Study on Micra Leadless PM (Micra CED) were published and confirmed the safety profile of this leadless device, comparing it also with the traditional transvenous PM. This was an observational study assessing complications, employment and outcomes of leadless VVI PM in the USA populations: 5746 patients with leadless VVI PM and 9662 patients with transvenous VVI PM were included in the analysis. There were no significant differences in the adjusted 30-day complication rate between the 2 groups (7.7% vs 7.4%, $p = 0.49$). Compared with patients with transvenous VVI, those with leadless VVI had a significantly higher proportion of pericardial effusion and/or perforation at 30 days (0.8% vs 0.4%; risk difference, 0.4; 95% CI, 0.1–0.7; $p = 0.004$). Analysing 6 months complication rates, patients implanted with leadless VVI PM had better outcomes than patients with transvenous VVI PM (hazard ratio, 0.77; 95% CI, 0.62–0.96; $p = 0.02$) [21].

The 2-years results of the Micra CED comparing 6219 leadless Micra TPS PM vs 10,212 transvenous VVI de novo PM implants in the US Medicare fee-for-service population demonstrated that the Micra TPS was associated with a 38% lower adjusted rate of reinterventions and a 31% lower adjusted rate of chronic complications compared with transvenous VVI pacing [22]. There was no difference in adjusted all-cause mortality at 2 years, probably reflecting the fact that leadless recipients are often older sicker patients with more comorbidities [23].

A recently published review also compared 3 leadless PM studies (n = 1284) to a VVI PM cohort (n = 14,330) and divided the analysis in short (<2 months) and long term (>2 months) complications [24]. In the first category conventional PM seemed marginally superior to PM (4.0% vs 4.8%) and again this was mainly driven by an increased risk of cardiac perforation and pericardial effusion with the leadless PM (1.5% vs 0.1%). Long-term complication rate was definitely in favour of leadless PM (0.2% in leadless system vs 3.1% in conventional PM); this difference is expected to become even more evident in future years, since these complications are quite exclusively associated to the device pocket and transvenous lead [24].

Lately, patients from three experienced leadless implant centres were propensity matched to 16 VVI-R patients from the FOLLOWPACE registry to evaluate safety profile at 2.2 years follow-up [25]. This study confirmed the reduction in mid/long-term rate of complications (0.9% in the leadless PM group vs 4.7% in the transvenous group, $p = 0.02$). Including in complications rate all PM advisory complications (related to Nanostim LCP), the benefit was no longer observed (complication rate 10.9% in the leadless PM group vs 4.7% in the transvenous group, $p = 0.063$) [25].

Table 1 (Ref. [10,15–22]) summarizes clinical studies published on both devices.

Table 1. Summarises available evidence on safety and efficacy of leadless pacemakers.

Study	FU (months)	Number of participants	Safety endpoint	Efficacy endpoint	Comments
Nanostim LCP					
LEADLESS [10,15]	12	33	31 (94%)	33 (100%)	
LEADLESS II [16]	6	300 (primary cohort; 527 total)	280 (93.3%)	270 (90%)	Primary cohort of 300 patients out of 527
LEADLESS Observational [17]	6	300 (post pause; 427 total)	285 (94.6%)	NA	Stopped for perforations and then resumed. Numbers relative to post pause enrolment
Micra TPS					
MICRA IDE [18]	6	725	696 (96%)	713 (98.3%)	
MICRA PAR 30 days [19]	1	792	780 (98.5%)	768 (97%)	
MICRA PAR 1 year [20]	12	1817	1768 (97.3%)	1762 (97%)	
MICRA CED [21]	1 and 6	1: 5746 6: 3726	–1: 5262 (91.6%) –6: 3607 (96.8%)	NA	1- and 6-months comparison with TV-PM
MICRA CED 2 years [22]	24	6219	5765 (92.7%)	NA	Comparison of chronic complications with TV-PM

LCP, leadless cardiac pacemaker; FU, follow-up; NA, not applicable; TPS, transcatheter pacing system; IDE, Investigational Device Exemption; PAR, Post Approval Registry; CED, Coverage with Evidence Development; TV, transvenous; PM, Pacemaker,

6. Current clinical applications

Historically, the only available pacing mode in both leadless PM was VVI-R, thus restricting its indication to a minority of patients who have chronic atrial fibrillation with concurrent atrioventricular block (AVB); patients with paroxysmal AVB with infrequent pauses and elderly subjects with complete AVB and a low level of activity may also be candidates [26].

After the introduction of the Micra AV, implantation of leadless PM may be considered also in patients whit AVB but preserved sinus node function [19]; particularly, AV synchrony is obtained through the accelerometer used for rate adaptiveness that is also capable of tracking atrial mechanical (not electrical) activity. The device recognizes 4 phases of atrial activity (Fig. 4): mitral/tricuspid valve closure (A1), aortic/pulmonic valve closure (A2), passive ventricular filling (A3), and atrial contraction (A4, also AM (A mechanical)) [27]. The Micra Accelerometer Sensor Sub-Study (MASS and MASS2) and Micra Atrial Tracking Using a Ventricular Accelerometer (MARVEL) studies [27] demonstrated the feasibility of tracking mechanical atrial activity to provide AV synchrony and the MARVEL 2 study confirmed the safety and efficacy of this algorithm [8]. The inherent limitation of tracking mechanical activity is that it relies on good atrial contraction, hence it may be suboptimal in patients where the atrial signal is poor. In addition to that, AV synchrony is not guaranteed at heart rates faster than 105 beats per minute because of fusion of the A3 and A4 components [28] and therefore in the next future refinement of the detection algorithm will be crucial for improved synchrony outcomes.

Currently, implantation of a leadless PM may be preferred in the following clinical scenarios:

(1) patients with no or difficult upper extremity venous access; the access site for the delivery of a leadless device is usually the femoral vein and there is no need for transvenous leads, thus overcoming this issue. In some very selected cases when femoral veins are not a viable option, a jugular approach has been used with satisfactory safety and efficacy outcomes [27].

(2) patients with previous cardiovascular implantable electronic device (CIED) infection; this group of patients is at risk of recurrent infection and they frequently wait many weeks as inpatients to have a definitive re-implantation [28]. Leadless devices could be a bridge or even a permanent option. In fact, there are no reports of leadless PM infection in clinical trials enrolling more than 3000 patients. Many possible explanations contribute to leadless PM resistance to infection and include the absence of a subcutaneous pocket and transvenous leads, reduced contact with skin and gloves and the minimized surface of the device [29]. Moreover, there are preliminary reports and data from the Micra PAR at 12 months regarding the extraction of infected transvenous systems and implantation of Micra during the same procedure, with no recurrence of infection at follow-up, supporting this potentially time-saving and safe approach [20,30,31].

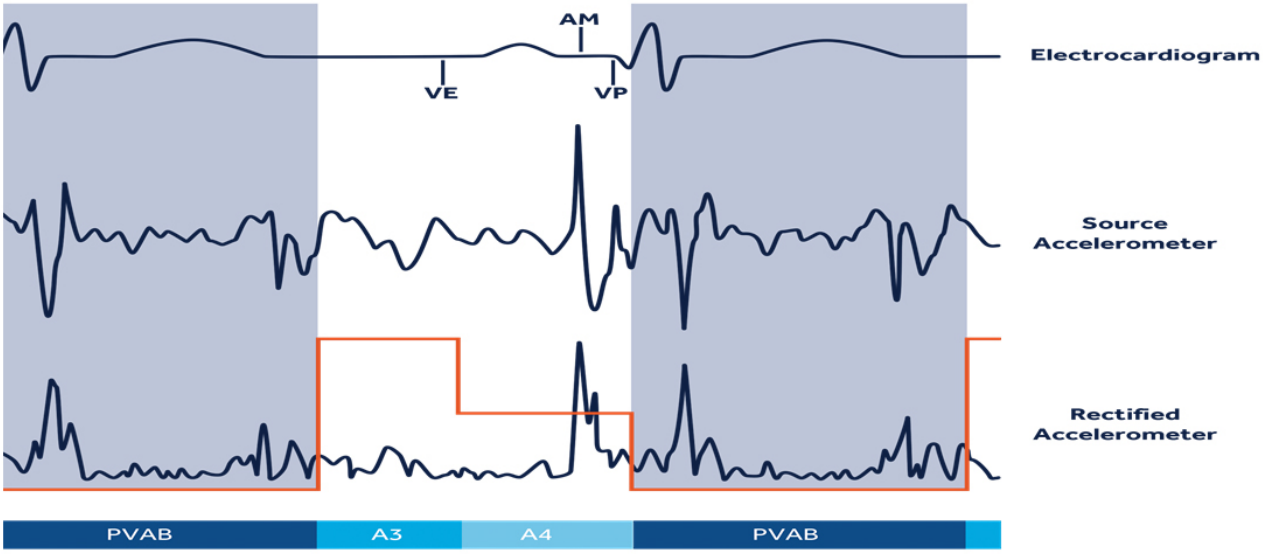

Fig. 4. Micra AV accelerometer signals. PVAB period: The A1 and A2 signals are blanked. No atrial sensing occurs during PVAB. A1: Start of ventricular systole, mitral and tricuspid valves close. A2: End of ventricular systole, aortic and pulmonic valves close. A3 detection window: Diastole, passive blood flow from atrium to ventricle (corresponds to E-wave on Doppler echo). Micra AV is designed to avoid detecting the A3 signal. A4 detection window: atrial systole, blood pushed into ventricles, corresponds to A-wave on Doppler echo. Courtesy of Medtronic Inc. Abbreviations: PVAB, post ventricular atrial blanking period.

(3) patients on haemodialysis, for both the aforementioned reasons of vascular access issues and risk of bacteriemia: in 201 patients on haemodialysis who underwent Micra implantation there was no evidence of device-related infection at 6 months follow-up [32].

(4) patients undergoing an "ablate and pace" procedure for uncontrolled atrial fibrillation (AF) with favourable results and the advantage of using only femoral venous access [33,34].

(5) leadless PM may serve as a promising future alternative in subjects who underwent tricuspid valve repair or replacement by a bioprosthesis and need single chamber pacing, preserving repaired valve from malfunction due to catheter "impingement". Conversely, crossing a mechanical prosthetic valve with the delivery sheath and leadless PM is contraindicated [26].

7. Future perspectives

7.1 Dual chamber leadless PM

An atrial Micra has been recently evaluated in sheep: the device prototype had flatter and shorter tines to reduce the risk of perforation in a chamber with even thinner walls than the RV. Implantation, retrieval, reimplantation and chronic pacing performance have all yielded positive results and in the next future the first human studies are expected [35].

7.2 Leadless PM and subcutaneous implantable cardioverter defibrillator (S-ICD)

There are several reports of the implantation of a leadless PM in conjunction with an S-ICD in individuals with lack of vascular access. No S-ICD oversensing nor interaction between the devices was observed at the time of implantation, during defibrillation testing and following an appropriate shock delivery [36,37]. In addition, a pre-clinical animal study demonstrated feasibility of the combination of an anti-tachycardia pacing (ATP)-enabled leadless PM with an S-ICD, with wireless unidirectional S-ICD to leadless device communication. ATP by the leadless PM was triggered by the S-ICD and effectively delivered [38]. After enrolling the first patient, the clinical study MODULAR ATP (NCT04798768) is currently under way to test the performance of the Modular CRM (mCRM™) System. This system is composed of a EMPOWER™ Leadless PM capable of ATP, paired with an EMBLEM™ S-ICD.

7.3 Leadless pacing in left ventricle (LV) for cardiac resynchronization therapy (CRT)

A leadless ultrasound-based endocardial PM for CRT could represent a valuable alternative in patients with difficult coronary sinus access or in non-responders to conventional CRT [39]. The wireless cardiac stimulation (WiCS) LV is currently being developed and enhanced. This system is composed of a subcutaneous pulse generator that communicates via acoustic energy (ultrasound) with a leadless pacing electrode fixed in the LV endocardium and that is delivered retrogradely to the LV. Initial experience in

the Wireless Stimulation Endocardially for Cardiac Resynchronization Therapy (WiSE-CRT) study showed successful implantation in 13 of 17 patients (76.4%) and good efficacy outcomes at 6 months follow-up in terms of shortened QRS duration and improved New York Heart Association (NYHA) class and LV ejection fraction (LVEF); significant complications, however, occurred, including 3 cardiac tamponades with one resulting in death [39]. The subsequent Safety and Performance of Electrodes Implanted in the Left Ventricle (SELECT-LV) study enrolled 35 patients non responders to classic CRT with higher implantation success (34 out of 35, 97.1%), favourable results in terms of LVEF increase and QRS shortening, but still a high rate of serious adverse events (39.5%) with 1 ventricular fibrillation caused by delivery catheter-induced ventricular ectopy which eventually caused patient's death. Furthermore, 2 subcutaneous pulse generator related infections were diagnosed [40].

The combination with leadless RV devices could bring to the realization of a totally leadless CRT-P or, with the addition of an S-ICD, even to leadless CRT-D, but confirmations of safety and efficacy of this technology are still pending.

7.4 Leadless His bundle pacing and left bundle branch pacing

His pacing (HBP) and left bundle branch pacing (LBBP) are innovative pacing modalities to enable cardiac resynchronization [41]. To date, there is no experience with leadless devices in this field but since the majority of them were implanted in septal position in latest studies [19], theoretically speaking there is a rationale to believe that future leadless devices could be designed to target the conduction system, attaching with a screw-in helix in the high septum and pacing in VDD mode.

7.5 End of life management: retrieval and battery recharge hypothesis

Given the novelty of leadless pacing, the ideal end-of-life strategy is still undefined. Battery duration is approximately 5 to 15 years, with a mean of 10 years, similar to that of transvenous devices [16,18] and therefore some patients may need more than one device in a lifetime. Retrieval of the previous leadless PM is a valid option to limit non-functional hardware inside the heart: Nanostim LCP has its own dedicated catheter with demonstrated efficacy [42] and there are reports of successful Micra removal using the introducer sheath and gooseneck snares [14,43]. In some cases, retrieval may not be a pursuable option due to encapsulation of the device and an abandonment strategy can be pursued since the small volume of leadless PM occupies less than 2% of the normal RV volume [44]. Clinical experience shows that in the majority of patients the systems are left in situ and no interactions have been observed between new and old devices so far; in those who undergo retrieval, the procedure can be carried out successfully also after a relatively long period after implant (up to 14 months) [43]. Self-recharging PM would solve the problem. There are pre-clinical descriptions of batteryless pacing using its own heart motion or solar energy captured by a transcutaneous module but there is still a long way to go [45,46].

8. Conclusions

Both leadless PM have shown safety and efficacy in initial trials but verification of these results in the long-term is still underway. Through continuous technological improvement and growing operator experience, complication rates are likely to decrease while indications will expand to larger groups of patients and beyond single chamber pacing. Randomized controlled trials enrolling present-time leadless and transvenous devices are necessary to compare both short- and long-term efficacy and safety profile of these new pacing devices.

Author contributions

GB, RS and MLNs designed the review article. All authors contributed to the editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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