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Mini Review

Leadless Pacemakers: Current and Future Applications

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Abstract

Leadless pacemakers: a brand new technology with a low rate of lead and pocket complications compared to traditional transvenous pacing. What it is known until now, current issues and future perspectives.

Keywords: Leadless Pacemakers; Micra; Nanostim; Pocket Infection; Lead Fracture

Abbreviations: PM: Pace Maker; ICD: Implantable Cardioverter Defibrillator; S-ICD: Subcutaneous ICD; CRT: Cardiac Resynchronization Therapy; FDA: Food And Drug Administration; IDE: FDA Investigational Exemption; PAR: Post Approval Registry; AV: Atrio- Ventricular

Introduction

Since its first prototype proposed in the 1970s [1], pacing technology has progressively developed sophisticated miniaturization of electronic component of device, abolished the need for leads, and greatly improved battery longevity in order to provide greater autonomy. Finally, in 2012, leadless pacemakers became a commercially available alternative to traditional transvenous/epicardial pacing first with the introduction of Nanostim (St. Jude Medical Inc.; now Abbott Medical Inc., Abbott Park, IL, USA) and shortly after with the Micra leadless pacemaker (Medtronic Plc, Minneapolis, MN, USA).

The main advantage of leadless pacing technology over traditional pacing technology should essentially be to avoid lead- and pocket-related complications. The incidence of post implant complications has been estimated as high as 10% [2] and it accounts for short term complications (such as pneumothorax, cardiac tamponade, pocket hematoma and lead dislodgement) and long term complications, mostly due to the vulnerable component of the system, the transvenous leads (such as insulation breaches and lead fractures), but also skin erosions, pocket or systemic infections, venous obstruction, tricuspid regurgitation and endocarditis.

Characteristics of Currently Available Leadless Pacemakers

The Nanostim LPS received a CE mark in October 2013, but it is still awaiting for the Food and Drug Administration (FDA) approval, while the Micra TPS was CE certified in 2015 and approved by the FDA in April 2016. The two self containing leadless devices share some common features, with some differences:

a) Discrete volume (1 cm3 for nanostim LPS versus 0,8 cm3 for Micra TPS); Nanostim is longer and narrower than Micra (42mm x 5.99mm vs 25.9mm x 6.7mm respectively).

b) Delivery system via a dedicated deflectable sheath (18F/21F, inner/outer diameter, for the LPS and 23F/27F for the TPS) advanced through the femoral vein under local anaesthesia and fluoroscopic guidance.

c) A small amount of contrast media is injected through the sheath to assess the correct position of the device inside the right ventricle.

d) Stimulation mode (VVI/R) with an integrated algorithm for rate response modality, based on a temperature sensor for Nanostim while Micra employs a three-axis accelerometer.

e) Retrievability of the device: the proximal end of both devices has been designed to recapture the system. Nanostim has a specially designed catheter with a single-loop snare system. Nanostim retrieval has a high success rate (up to 88%), and it remains this high also in older devices in selected cases. Micra retrieval requires the use of a goose-neck catheter introduced inside a steerable sheath or through the delivery system. The success rate appears

to be 60-80%. There is some concern, and poor documentation, about retrieval of older devices due to early encapsulation so abandonment seems to be a suggested strategy.

f) Magnetic Resonance Imaging (MRI) conditional: both devices have been proved to be safe at 1.5-3.0 T.

g) The fixation mechanisms are different between the two Leadless PMs: LPS employs a non-retractable screw-in helix while the Micra TPS employs flexible curved nitinol tines.

h) The communication system for interrogation and programming of the leadless pacemaker is accomplished through conductive technology for the Nanostim with 5 ECG surface electrodes to apply subliminal 250 kHz pulses, while the Micra uses conventional radiofrequency.

Clinical Data

Nanostim LPS

The LEADLESS trial [3] was the first prospective, nonrandomized, single-arm, multicentre study to evaluate efficacy and safety of the Nanostim LPS. 33 patients were enrolled between December 2012 and April 2013. The primary safety endpoint was freedom from serious adverse events at 90 days. The overall rate of complication-free cases was 94% with only one serious adverse event reported (a 70 year old man with chronic atrial fibrillation who died after cardiac tamponade during which urgent cardiac surgery was needed and an ischemic stroke in the postoperative phase was developed). The second safety endpoint was implant success rate, which occurred in 97% of the patients (32 out of 33). The electrical parameters improved during the 3 month follow up period and no adverse event requiring the revision of the device occurred. Complication incidence, electrical features and rate response characteristics were observed in a longer follow up period of 12 months [4] in 31 patients.

During this mid term follow up the LPS confirmed a good electrical performance and no adverse events were observed. The FDA investigational exemption (IDE) trial, LEADLESS II [5], was a prospective, single arm, multicentre study on 526 patients. Primary efficacy endpoint was an acceptable pacing threshold and R-wave amplitude and was reached by 270 of the 300 patients in the primary cohort. Primary safety endpoint was defined by the standard ISO 14555 3.36 definition of Serious Device Adverse Effect at 6 months of follow up; device related serious adverse events occurred in 6,5% of patients and included cardiac perforation (1,3%), device dislodgement (1,7%), elevated pacing threshold requiring replacement (1,3%) and vascular complications (1,3%).

Noteworthy is that a first battery advisory with the Nanostim LPS was issued in 2016 by the manufacturer (an abrupt battery depletion in about 0,5% of patients within 29 and 37 months post implant) and then a second safety advisory was raised for docking button detachments observed in 4 out of 1423 patients implanted until April 2018. For these reasons Nanostim implantation was stopped.

Micra TPS

The FDA IDE Micra Transcatheter Pacing Study [6] was a prospective, non randomized, single arm, multicentre study enrolling 725 patients. The primary efficacy outcome was an acceptable pacing threshold at 6 months of follow up. It was reached in 98,3% of the 297 patients who reached the 6-month follow up.

The primary safety endpoint was freedom from device and procedure related adverse events (defined as "Major Complication" in the study). 28 events occurred in 25 patients: one death due to metabolic acidosis related to prolonged procedural time (implant plus atrioventricular node ablation) was observed. No device macroscopic dislodgement was observed and electrical parameters tended to improve over time. The Micra TPS Post-Approval Registry [7] was a prospective, non randomized, multicentre registry which aims to evaluate safety and effectiveness of the TPS in a real-word setting and it is still ongoing. An interim analysis of 705 patients enrolled so far, demonstrated an elevated successful implantation rate (99,6%). 13 serious adverse events in 12 patients occurred in the 30-day follow up period, most of them related to the percutaneous access.Overall 5 pericardial effusions or perforations were observed, but only 1 met the criteria to be considered a major complication. None of the deaths registered were attributable to the Micra TPS. Comparable results were observed in another real-word setting PAR during a mid-term follow up period of 12 months. Noticeably, the risk of major complications was 63% lower than that observed for transvenous conventional implantation at 12 months [8].

Comparison Between the Leadless Pacemaker and Leadless PM Versus Conventional VVI Pacing

Nanostim LPS and Micra TPS showed overall comparable results in terms of safety and efficacy. Leadless pacemaker implantation is indicated only in conditions where right ventricular pacing and sensing are needed (VVI/VVIR mode): atrial fibrillation with atrioventricular (AV) block; II o III degree AV block with a low level of physical activity or short expected lifespan; sinus bradycardia with infrequent pauses. Leadless pacing modality has also been proposed for patients with an unfavourable venous anatomy (e.g venous occlusion or thrombosis) and in patients with high infection risk (e.g. previous infection at the implant site, chronic kidney disease with the need for dialysis). The leadless system carries a certain risk of femoral vascular complications, which is unique to the percutaneous delivery system. The overall incidence is however low and comparable between the systems.

Another possible complication is device dislodgement: the overall incidents observed in the IDE study and PAR was low, but

favours the Micra system (0,06% versus 1,1% in the LEADLESS II trial). Cardiac injury incidents also appeared similar for the two devices in the IDE studies (1,5%), but differences were observed in the real word setting. For example, in the European LEADLESS Observational Study [9] 6 major cardiac injuries for Nanostim LPS were reported among the first 147 patients enrolled, 2 of them leading to death, and thus causing the temporary interruption of the study. A possible explanation is the different fixation mechanisms (screw-in helix) of the Nanostim system, which requires a careful balance between adequate fixation in order to avoid dislodgement and at the same time avoidance of excessive penetration with the subsequent risk of myocardial perforation. This could be achieved through adequate operator training. A comparison between transvenous and leadless systems was investigated using a large VVI-PM recipients population (14,330 patients from 10 different studies) compared with the whole population from the leadless pacing trials (1284 patients). The short term (< 2 months) complication rate was slightly higher for leadless pacemakers (4,8% versus 4,1%), cardiac perforation and pacing threshold elevation being more frequent in this group (1,5% vs 0,1% and 0,5% vs. 0%, respectively), while acute lead or device dislodgement rates were similar and very low [10].

The Micra Global Clinical Trial was a prospective, non randomized, single arm worldwide trial, which aimed to evaluate safety and efficacy of the Micra TPS mid-term (6 months) and long-term (12 months), in terms of freedom from major complication and electrical performance [11], comparing the Micra cohort with a historical "VVI modality" cohort. In brief, a safety endpoint was achieved without major complications (a rate of 96% complication-free at 12 months and a 48% reduction in 1-year complication rate, with an 82% decrease in revision procedures, a 48% lower 1-year complication rate). Electrical performance was excellent throughout the 24 months. To date, no long term performance and safety data on leadless pacemakers is available and RCTs comparing this new technology with traditional transvenous/epicardial pacing are lacking. Retrievability of leadless systems is easily feasible during the implantation procedure, before unlocking the tethering lead, and the procedure is well described by the manufacturer. Further concerns have been raised upon retrieval after the "acute" phase, when fibrosis develops around the distal end of the device. Few cases of retrieval of the Micra TPS have been described [12], demonstrating that retrieval is feasible during an early phase (a range of 1-61 days) post implant using a percutaneous gooseneck snare. Our group described a successful retrieval of a Micra TPS after 40-days from implantation, due to increased pacing threshold secondary to micro-dislodgement [13].

Future Perspectives

Single chamber pacemakers serve a minority of PM recipients (around 15-30%). Therefore, efforts have been made to extend leadless technology to multisite pacing and cardiac resynchronization therapy, through the development of multicomponent and communicating devices. Of note, is the wireless cardiac stimulation (WiCS)-LV system, which consists of two components: a subcutaneous ultrasound transmitter and an endocardial left ventricle electrode, which converts US frequencies into electrical pacing impulses. The device can communicate with any other traditional endocardial system (PM, ICD, CRT) to trigger synchronous LV pacing with RV activation (sensed or paced) [14,15]. Another possible application of leadless pacemakers is within defibrillation therapy, for instance combined with subcutaneous ICD (s-ICD), with the aim to erogate antitachycardia pacing. Further investigation in these fields is needed.

Conclusion

Leadless pacemakers are a new promising technology, the use of which is spreading in the clinical practice due to the possibility of avoiding leads- and pocket-related complications of transvenous pacing. It is mandatory to further investigate long term performance, safety and retrievability of these devices in ad hoc randomized clinical trials, in comparison with conventional endocardial pacing. Their field of application is still confined to single-chamber pacing. In the future, multicomponent, wireless, leadless systems could possibly enable integration between multisite pacing, resynchronization therapy, defibrillator therapy and even heart failure monitoring.

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