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Leadless pacemaker 5-year outcomes: good news?

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In the last 10 years, leadless pacemaker (PM) therapy has moved beyond the experimental phase and has become an established therapeutic option. A substantial body of data are now available, even with medium-length follow-ups, suggesting that leadless PMs are associated with fewer infections and fewer overall complications, particularly in the long term, compared with transvenous PMs. The introduction of VDD(R) pacing and, more recently, DDD(R), has expanded the indication area of these devices to a significantly larger number of patients. High costs, limited experience with replacement and the lack of randomized studies still limit their widespread adoption. However, for many patients, the leadless PM already represents the first therapeutic choice.

Introduction

Traditional transvenous electrostimulation, despite its constant progress, is still burdened by a significant rate of complications, mainly related to the electrocatheters and the pocket in which the device is housed. Short-term complications range between 9.5 and 12.6% and are mainly caused by electrode dislocation and, less frequently, by pocket haematoma, pneumothorax, or cardiac tamponade. Long-term complications, on the other hand, constitute a further 9% and are caused by electrocatheter malfunction, endocarditis, venous obstruction, severe tricuspid insufficiency, pocket problems (infection and skin erosion), often require reoperation and are possible causes of an increase in morbidity and mortality. Leadless pacemakers (PMs) were introduced precisely to provide a possible solution to these problems by eliminating the two main sources of complications: the electrocatheters and the pocket. At the moment, there are two devices available: Micra and Aveir. The latter is the evolution of Nanostim, the first leadless PM to be marketed but then withdrawn due to problems related to early and unpredictable failure of the battery and the fixing system. Both have received the European Community mark and Food and Drug Administration approval. These devices are implanted in the wall of the right ventricle (RV), at the septum or apex, where they reach, via a catheter, through the femoral vein and the inferior cava. Both are Magnetic Resonance Imaging Conditional, the Aveir at 1.5 T, the Micra also at 3 T.

Indications

The first devices were able to stimulate and sense the electrical activity of the ventricle only (VVI mode) and therefore the main indication for their use was atrial fibrillation with low ventricular response. The leadless PM was however also taken into consideration in the case of paroxysmal atrioventricular blocks, sinus node disease, or syncope, in which a high percentage of pacing was not expected. The rapid technological progress of these devices has however introduced, with the Micra AV,[1] the possibility of VDD pacing (the ability to sense the electrical activity of both the atrium and the ventricle allows ventricular pacing to be co-ordinated with atrial activity) and, with the Aveir DR,[2] DDD pacing (pacing and sensing in both the atrium and ventricle). Regardless of the type of bradyarrhythmic problem present, leadless PM should also be considered in patients at high risk of systemic infection or who have already experienced an infection of an implantable cardiac device; when the upper central venous system is damaged, as in the case of previous transvenous PM implantation, infection of indwelling catheters, thoracic surgery, radiotherapy for thoracic tumours or trauma and, finally, in case of

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dialysis, both to save the venous accesses necessary for fistulas and because the increased rate of transient bacteraemia during dialysis can lead to haematogenous infection of the electrocatheters. Leadless PMs, on the other hand, are less prone to such infections, probably due to their small size and being encapsulated within the heart wall. Other possible indications are subjects with repair or replacement of the tricuspid valve with a bioprosthesis, to preserve it from damage due to the electrocatheter crossing it, candidates for 'ablate and pace', in which the entire procedure could be performed with only the femoral access and, finally, subjects with cachexia or thin skin who, due to these conditions, present a higher risk of complications related to the subcutaneous pocket and the electrocatheters.

5-year results

Data on the performance of these devices in the short term (1–6 months) have been available in the literature for almost 10 years,[3–7] which overall showed a high implant success rate, good electrical measurements, and a lower complication rate compared with transvenous PMs. However, data on more extensive follow-ups were lacking, but fortunately, these have now become available.

The Micra PAR[8] is a prospective, non-randomized, real-world registry designed to follow patients for 9 years after implantation, to evaluate major complications related to the device or the procedure, system revisions for any reason, and all-cause mortality. Data on the first 5 years of follow-up have recently been published, in which, among other things, major complications and system revisions were compared with a data set (with a follow-up limited to 36 months) of 2667 patients with transvenous dual-chamber PMs (historical PM-TV cohort). One thousand eight hundred and nine patients who underwent leadless PM implantation were followed for a mean follow-up of 51.1 months, patients had a mean age of 79 years at implantation, 38.8% were female, and had multiple comorbidities. The Micra VR device was successfully implanted in 1792 (99.1%) of the 1809 patients, with the right ventricular septum being the most common implant site (65.1%). A total of 85 major complications were reported in 79 patients during the entire follow-up, for a 5-year rate of 4.5% [95% confidence interval (CI): 3.6–5.5%]. Most major complications (58.8%, 50/85) occurred within 30 days of implantation and largely included procedure-related events such as thrombosis, groin puncture problems, pericardial effusions/perforations, or capture and elevated threshold problems. Major long-term complications included capture and elevated threshold problems (14 after the first 30 days), PM syndrome (seven after the first 30 days), and PM-induced cardiomyopathy (five after the first 30 days). Nine cases of infection were reported, five of which met the criteria for a major complication. None of the infection events resulted in device removal. There were 676 deaths from any cause during the follow-up period, for a 5-year mortality rate of 39.5%. Of these deaths, five were procedure-related (including two due to cardiac perforation), 35 were classified as sudden cardiac death, 113 were non-sudden cardiac death, 345 were non-cardiac deaths (including 15 from COVID-19), and 178 had an unknown classification.

There were 85 revisions in 82 patients with a 60-month rate of 4.9% (95% CI: 3.9–6.1%). The three most common reasons for revision were device upgrade (to PM DDD or cardiac resynchronization therapy in 35 patients), elevated pacing threshold (26 cases in 25 patients), and battery depletion in the setting of elevated thresholds (12 patients). The most common actions taken after revision were device reprogramming to OOO mode (66 cases in 65 patients) or device explantation (11 cases in 11 patients). In four cases, the Micra VR was reprogrammed for backup pacing (VVI-40) after upgrading to a transvenous system. In 13 patients, a second Micra device was implanted in the RV abandoning the original Micra. No adverse events related to the interaction of the two devices were reported during a median follow-up of 13 months.

Over the 5 years following implant, the cumulative rate of patients with the first device out of service due to elevated pacing threshold or battery depletion was 2.1% with an additional 2.7% of devices out of service for other reasons (e.g. upgrade). The remaining 95.2% of patients instead had the initial device still active at the time of death (37.5%) or at the last follow-up (57.7%).

For pacing parameters, the mean capture threshold increased from 0.67 ± 0.55 V at 0.24 ms at implant to 0.70 ± 0.44 V at 0.24 ms at 60 months. The mean pacing impedance was $727 \pm 173\ \Omega$ at implant and $533 \pm 101\ \Omega$ at 60 months. The mean R-wave sensing amplitude was 10.7 ± 5.0 mV at implant and 13.1 ± 5.7 mV at 60 months. The median per cent ventricular pacing among the 1030 patients with available data was 78.9%. Based on device use conditions in 920 patients, the mean predicted residual battery longevity after 5 years of follow-up was an additional 6.8 years, with at least five additional years of life remaining in 83.8% of patients.

Compared with the historical TV-PPM cohort, in the first 36 months after implantation, the rate of major complications for Micra VR patients was 4.1 vs. 8.5% (HR: 0.47, 95% CI: 0.36–0.61, $P < 0.001$). Finally, the rate of all-cause system revision over 36 months for Micra VR patients was 3.2 vs. 6.6% in the historical TV-PPM cohort [hazard ratio (HR): 0.47, 95% CI: 0.34–0.65, $P < 0.001$].

The study data are consistent with those previously reported in series with shorter follow-up and, overall, highlight the reliability of the Micra wireless PM, which has low rates of complications and system revisions (both <5%) over the 5-year follow-up. They also confirm that most major complications occur within the first 30 days, with only slight increases beyond 12 months, mainly related to high threshold events. In the 3 years in which comparison with the PM-TV cohort was possible, a reduction of 53% was also confirmed in both cases, both in major complications (driven by the absence of dislocations and revisions of the leads) and in system revisions. Another notable finding that emerged is the low (2%) rate of upgrade to cardiac resynchronisation therapy despite a high median pacing percentage (78.9%). This low upgrading rate is surprising since the incidence of pacing-induced cardiomyopathy is commonly reported in a range from 6 to 39%. The mid-high septal position of the leadless PM, which was the implant position in 65% of patients in this cohort, could be a possible explanation for this finding. The third aspect to highlight is the absence of infections requiring device removal. In this study, almost all infections observed involved soft tissue and responded well to antibiotics or conservative management. Finally, the study also provides information on how to proceed when the battery needs to be revised or deleted. In most patients in this cohort, the old device

was abandoned (72/85), deactivating it (OOO mode) or, in a small minority, programming it as a backup system. A new Micra was implanted in 13 patients and no interaction with the previous device was observed nor was any impairment of right ventricular function noted. Ten patients (the oldest of which was 4 years old) still had their devices (the oldest of which was 4 years old) successfully removed and a new one implanted. These data therefore confirm that devices that have been implanted for several years can be removed. However, since device removal can be difficult and potentially risky due to the development of fibrotic tissue and considering that patients undergoing Micra are typically elderly and with significant comorbidities, avoiding unnecessary extraction may be the preferable strategy at the time of revision or at the end of the device's life cycle.

The high 5-year mortality rate observed in the study (39.5%) is not unexpected. This cohort had a mean age of 76 years and multiple comorbidities, for example, 21% of patients had chronic kidney disease, 8% were on dialysis, and 26% had diabetes. It is also possible that patients preselected for a lead-free device are inherently a 'sick' population due to the perceived low risk of infection with this technology. Finally, the predicted median battery longevity of patients by the end of the 5-year follow-up was 6.8 years, consistent with the initial projection of a median battery life of 12.1 years observed in the Micra VR IDE study.[9]

Further 5-year data, consistent with the previous ones, come from a Dutch retrospective cohort study[10] on 179 patients treated with Nanostim or Micra VR, followed for a mean follow-up of 44 ± 26 months, with, however, a subgroup of 66 subjects with $\geq$5 years of observation. Net of the recalls to which nanostim was subjected, which we mentioned previously, 4% ($n = 7$) of major complications and 10% of total complications (major and minor) were observed at 5 years. The seven major complications occurred on average 10 days (range 0–88 days) after implantation, with no significant differences between the two devices used. The capture threshold was $\leq$2 V at the time of implantation in 98% of patients and remained stable thereafter (increase $\leq$1.5 V) until the last follow-up visit, in an equal percentage. R-wave amplitude increased over time ($P = 0.002$) and impedance decreased ($P < 0.001$). Pacemakers extraction was attempted in 34 patients and was successful in 30 (88%). All 34 devices were Nanostim and had been implanted for a mean of 37 ± 22 months. Eighty-three patients (46%) died, a mean of 34 ± 23 months after implantation, but none of the deaths were considered device-related. Of note, no device infections occurred in this study; no complications requiring surgery were observed after the first 88 days after implantation; and, finally, long-term stability of pacing parameters was confirmed, unlike transvenous PMs where the pacing threshold tends to increase slowly over time.

Conclusions

Over the past 10 years, leadless PM therapy has moved beyond the experimental phase and has become an established therapeutic option. A substantial body of data, even with medium-length follow-ups, is now available, suggesting that single-chamber VVI(R) leadless PMs are associated with fewer infections and fewer overall complications, particularly in the long term, compared with transvenous PMs. Acute perforations may be more frequent and serious, but their risk is reduced with training and increased operator experience. The introduction of VDD(R) and, more recently, DDD(R) pacing has expanded the indication area of these devices to a significantly larger number of patients. High costs, limited experience with replacement, and lack of randomized studies currently still limit their widespread adoption. However, for many patients, such as those undergoing haemodialysis, with limited vascular access or at high risk of endocarditis, leadless PMs are already the first choice of treatment.

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Data availability

No new data were generated or analysed in support of this research.

Disclaimer

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