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par

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TITRE

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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur et
de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent,
et n'exigerai jamais un salaire au-dessus de mon travail.

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corrompre les mœurs ni à favoriser le crime.

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rendrai à leurs enfants
l'instruction que j'ai reçue de leurs pères.

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promesses. Que je sois couvert
d'opprobre et méprisé de mes
confrères
si j'y manque.

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To the moon… and back.

RESUME

Introduction : L'efficacité et la sécurité de la stimulation cardiaque sans sonde comme alternative aux pacemakers conventionnels a été montrée, avec une évolution récente par l'ajout d'algorithmes permettant une synchronisation atrio-ventriculaire. L'objectif de l'étude était de rapporter l'expérience avec ces deux générations de pacemakers sans sonde dans un centre à haut volume d'implantation.

Méthodes : Cette étude observationnelle rétrospective a inclus les 400 premiers patients ayant bénéficié de l'implantation d'un stimulateur cardiaque sans sonde au CHRU de Tours depuis 2015. Les évènements évalués au cours du suivi étaient les complications et les paramètres électriques, en comparant les pacemakers sans sonde de première (Micra VR) et de seconde génération (Micra AV). La synchronisation atrio-ventriculaire a été évaluée chez les patients porteurs d'un Micra AV. Le recueil des données s'est fait par consultation des dossiers médicaux.

Résultats : Parmi les 400 procédures, on recensait 328 Micra VR et 72 Micra AV. Le taux de succès d'implantation était de 99.5%. 87.5% des patients étaient sortis de l'hôpital le lendemain de l'intervention. Le seuil de stimulation est resté stable et inférieur à 2 V chez 96.5% des patients. Le taux de complications péri-opératoires était de 3.5%. Le suivi était comparable entre les deux groupes. Parmi les Micra AV, la synchronisation atrio-ventriculaire s'améliorait significativement entre la sortie et la première visite (indice de suivi 72% vs 54%, $p = 0.02$) et 40 patients sur les 50 avec une stimulation ventriculaire significative ont présenté une bonne synchronisation atrio-ventriculaire (> 66%). Un ratio E/A sur le flux Doppler trans-mitral en échocardiographie inférieur à 1 en préopératoire était le seul prédicteur d'une bonne synchronisation atrio-ventriculaire en analyse multivariée ($p = 0.04$).

Conclusion : La stimulation cardiaque sans sonde est une alternative efficace et sûre à la stimulation cardiaque conventionnelle. L'apparition d'un algorithme de synchronisation atrio-ventriculaire permet un élargissement des indications d'implantation pour les stimulateurs cardiaques sans sonde.

Mots-clés : stimulation cardiaque sans sonde, complications péri-opératoires, synchronisation atrioventriculaire

ABSTRACT

Introduction: Efficacy and safety of leadless cardiac pacing as an alternative to conventional transvenous cardiac pacing has been proven, and a recent evolution has allowed for atrioventricular synchrony through the addition of electronic algorithms. The aim of this study was to report the experience of a high-volume implantation center with these two generations of leadless pacemakers.

Methods: This retrospective observational study has included the first 400 patients who underwent an implantation of a leadless pacemaker at the Tours University Hospital (France) since July 2015. Complications and electrical parameters during follow-up were evaluated, comparing patients implanted with first (Micra VR) and second generation (Micra AV) leadless pacemakers. Atrioventricular synchrony was evaluated in patients implanted with Micra AV. Data were collected by a review of medical files.

Results: Among 400 procedures, there were 328 Micra VR and 72 Micra AV implanted. Implantation success rate was 99.5%. 87.5% of patients were discharged the day after the procedure. Pacing threshold remained stable and inferior to 2V in 96.5% all patients. Peri-operative complication rate was 3.5%. Follow-up was comparable between the two groups. Among patients implanted with Micra AV, atrioventricular synchrony improved significatively between discharge and first follow-up (tracking index 72% vs 54%, $p = 0.02$) and 40 patients out of 50 with a significant pacing burden presented with high atrioventricular synchrony (> 66%). Pre-operative mitral E/A ratio lower than 1 in echocardiography was the only predictor of high atrioventricular synchrony in multivariate analysis ($p = 0.04$).

Conclusion: Leadless cardiac pacing is a safe and efficient alternative to conventional transvenous cardiac pacing. The emergence of an algorithm to improve atrioventricular synchrony allows for a broader range of indications for leadless pacemakers.

Keywords: leadless cardiac pacing, peri-operative complications, atrioventricular synchrony

TABLE DES MATIERES

ABBREVIATIONS

AF: Atrial fibrillation

AV: Atrioventricular

EP: Electrophysiological

MRI: Magnetic Resonance Imaging

OR: Odds Ratio

ROC: Receiver Operating Characteristics

TAVI: Transcatheter Aortic Valve Implantation

TM: Trademark

TPS: Transcatheter Pacing System

INTRODUCTION

Historical Background

Intracardiac pacing has been developed for more than 60 years and is the only effective long-term treatment for patients presenting with symptomatic and irreversible conduction disorders, showing great benefits on morbidity and mortality. Since the very early years, cardiac pacing technology has made significant progresses towards smaller, more durable, and more reliant pacing systems.

Conventional pacing devices nowadays consist of an extravascular pulse generator inserted in a subcutaneous pocket below the clavicle, with one or more leads positioned in the desired heart cavity through supracaval venous system.

Despite being effective in its main objective to substitute for native conduction system, conventional pacing therapy is burdened by several complications. Most of them are inherent to the design of the device as they are related to the pulse generator and the lead, with complications rates as high as 10 to 16% of transvenous pacing systems implantations[1-4].

The most vulnerable part of the pacing system is the lead, subjected to repetitive mechanical stress, exposed to dislodgement, fracture, insulation defect, connector issues, and infection. Other peri-procedural complications include pneumothorax, cardiac perforation, pocket hematoma and skin erosion, also eventually leading to infection.

Those complications are more likely to happen in fragile patients, with active infection, renal disease, but also in females and low body mass index patients[5-6], and have high costs mostly driven by daily supplements for the intensive care unit[7-8].

Over the past decade, leadless pacemakers have been developed as an option to avoid such complications. Two systems have been developed, the Micra Transvenous Pacing System (Medtronic Inc, Minneapolis, MN, USA) and the Nanostim™ (St. Jude Medical Inc., Saint Paul, MN, USA; now Abbott Medical Inc. Abbott Park, IL, USA) – now the Aveir™ – which was the first implanted in man in 2014.

Of those two systems, only the Micra Transvenous Pacing System is approved on the European market and available in day-to-day practice.

The Micra Transvenous Pacing System consists of a small cylindrical capsule (0.8 cc, 2 grams) delivered directly into the right ventricle through a venous femoral approach, with four integrated self-expanding electrically inert nitinol tines allowing for passive fixation. All its components are MRI compatible.

Leadless pacemakers have been shown to be a feasible and safe option in selected patients[9-10], notably in infected patients or patients at high risk for infection[11], and in dialyzed patients[12]. Large registries have demonstrated a high implantation success rate, with complications rates in the first two months similar to those of transvenous pacemakers (4 to 5%) but a significantly lower incidence of long-term complications and pacemaker revisions[13-15].

Electrical parameters have also been proven to be stable over time, providing an estimated battery life of approximately twelve years[16].

Complications differ from those of transvenous pacemakers, as they include more cardiac perforation, and a risk of vascular complications inherent to the venous femoral approach, but virtually no infection.

Mostly used at first in patients requiring a single-chamber device, leadless pacemakers have also been implanted in patients with complete atrioventricular block but who either could not undergo a conventional transvenous implantation, or who presented with an active infection or at least significant comorbidities.

Several studies have shown a benefit of dual chamber pacing versus single chamber pacing in patients with high-grade atrioventricular block on quality of life and hemodynamics[17-21], but with no difference on mortality or cardiovascular events[22-24]. As such, if feasible, dual chamber pacing is generally recommended in patients with high-grade atrioventricular block to improve atrioventricular synchrony.

The first generation of leadless pacemakers however only provided single-chamber ventricular rate responsive pacing, prohibiting the possibility of atrioventricular synchrony.

VDD Leadless Pacemaker

Considering this, a second generation of leadless pacemakers has been developed and the Micra AV leadless TPS (Medtronic, Minneapolis, MN) was released in February 2020, with nominal programming in a ventricular-pacing atrial-tracking mode (VDD). Second generation Micra Transvenous Pacing System consists of the same device as its predecessor – with a similar implantation procedure – enhanced by the presence of an algorithm designed to sense atrial mechanical contraction, as described in the Marvel 2 Study[25].

The Micra device incorporates a 3-axis accelerometer for rate response. A single axis accelerometer vector or a combination of vectors can be used to detect the atrial contraction, with an auto-setup algorithm recommending the best accelerometer vector combination for atrial contraction.

The accelerometer signal typically exhibits 4 distinct segments of cardiac activity. The accelerometer signal is filtered and rectified prior to detection.

The two most important signals detected are labelled A3, corresponding to passive atrial filling, and A4, corresponding to the atrial kick.

The algorithm incorporates a post-ventricular blanking period and a dual threshold detection method. The first threshold (A3 threshold) that occurs early is used for detecting the atrial contraction at higher heart rates when A3 and A4 signals merge ("A7" signal). The second threshold (A4 threshold) triggers ventricular pacing on isolated A4 signal. The timing of the A3/A4 threshold transition (A3 window end) is also programmable. Because of the importance of the A3 window, a telemetry marker (VE) is displayed at the end of the A3 window.

The algorithm also includes a rate smoothing feature allowing maintenance of AV synchrony in case of intermittent A4 undersensing.

The algorithm provides two mode-switch algorithms to switch out of VDD mode during periods of intact AV conduction and high patient activity. The intact AV conduction mode-switch periodically switches to VVI mode at 40 bpm to search for AV conduction and will return to VDD if ventricular pacing occurs. The activity mode-switch monitors the accelerometer-based sensor rate and will switch to VVIR, if the sensor rate is at the patient's activities of daily living rate or higher and at least 20 bpm higher than the patients VDD tracking rate.

Device programming optimization aims to improve atrial mechanical sensing by adjusting the different signal discriminators for ventricular passive filling (A3) and atrial contraction (A4).

Previous proof-of-concept studies and feasibility studies demonstrated that this accelerometer-based atrial sensing was feasible and significantly improved atrioventricular synchrony in patients with sinus rate and high-grade atrioventricular block[26-27].

Study Objectives

In this study, we report a 7-year Micra implantation experience in the CHRU of Tours, both with first and second generation of those leadless pacemakers, assessing the safety and efficacy of this procedure over time in our high-volume center. We sought to evaluate the electrical performance of Micra implanted with the downloaded atrioventricular synchrony algorithm, focusing mainly on the proportion of atrioventricular synchrony and its evolution over time, and trying to identify predicting factors for high atrioventricular synchrony.

METHODS

Study design and patient population

This observational retrospective single center cohort has included the first 400 consecutive patients with a Micra implantation attempt in the CHRU of Tours (France), with procedures ranging from July 2015 to May 2022. The first implantation of a second generation Micra occurred in May 2020.

Baseline characteristics were collected from medical files on the date of admission and hospitalization records.

Pre-implantation echocardiography was not mandatory, and when performed was not standardized as it often occurred in an intensive care unit context.

Given the observational nature of our study, patient consent was not sought for this analysis as the participation to this study did not require their implication nor had any impact on their follow-up. All patients however provided written informed consent before Micra implantation. Most of the patients implanted with second generation Micra Transvenous Pacing System were also included in a multicenter prospective cohort (Micra AV study) for which they provided written informed consent.

Implantation procedure

The implantation procedure was done according to standard practice[28].

The Micra Transvenous Pacing System was implanted through a femoral venous approach using a 23-F inner diameter and 27-F outer diameter delivery sheath, advancing through the tricuspid valve to the right ventricle with a steerable catheter under fluoroscopic control.

Passive fixation was then obtained at a selected site in the right ventricle through the deployment of the nitinol tines. If electrical parameters were considered adequate (impedance, pacing capture thresholds, R-wave amplitude), the Micra Transvenous Pacing System was permanently released as the tethers were cut from outside.

The procedure and the device were identical for first and second generation Micra Transvenous Pacing System.

Patients were monitored for at least 24 hours following the procedure, with continuous telemetry monitoring, and were discharged after verification of the puncture site, electrocardiogram, chest radiography, and after ensuring of the absence of pericardial effusion.

Follow-up

After implantation, patient and device status were reported at discharge, at one month and then at least once a year. Data were censored at the time of last known follow-up.

Clinical and electrical data were collected from consultation records, and electrical parameters for second generation Micra Transvenous Pacing System were also collected from reviewing pacemaker interrogations which were stored as part of the Micra AV study.

Pacemaker setting was at the physician's discretion at first, and programming strategy for optimizing atrioventricular synchrony in second generation Micra was helped as of December 2021 by expert consensus programming guidelines issued by Medtronic.

Outcomes

Safety and efficacy were evaluated and then compared between patients implanted with Micra VR and Micra AV. Safety was evaluated by assessing peri-procedural and late complications, and efficacy was evaluated by assessing electrical parameters in both groups.

A focus was made on second generation Micra Transvenous Pacing System to evaluate the efficacy of the algorithm for atrioventricular synchrony.

Total atrioventricular synchrony was defined as the sum of Am-Vs (spontaneous beats tracking an atrial mechanical contraction), Am-Vp (paced beats tracking an atrial mechanical contraction) and AV conduction mode switch percentages.

The impact of Micra AV on atrioventricular synchrony was assessed in patients with at least 20% of ventricular pacing by the evaluation of the tracking index, defined as the proportion of ventricular pacing that tracked an atrial mechanical contraction as shown during pacemaker interrogation, calculated as the Am-Vp percentage divided by total Vp percentage. Arbitrarily, a tracking index higher than 66% was considered as high atrioventricular synchrony.

Patients with less than 20% ventricular pacing and patients programmed to VVI mode during follow-up were excluded from this analysis.

Predictors of atrioventricular synchrony

We finally aimed to determine predicting factors for high atrioventricular synchrony.

Statistical analyses

Analyses were performed using JMP software version 9.0 (SAS Institute Inc., Cary, NC, USA) and online via biostatgv.sentiweb.fr.

Continuous data were presented as mean ± standard deviation if normally distributed, median (interquartile range; [min-max]) if not. Categorical data were reported as frequencies and percentages. Comparisons used the $\chi 2$ or Fisher's exact test for categorical variables and Student's t test or Mann-Whitney-Wilcoxon test, when appropriate, for continuous variables. Student's t test for paired samples was used for the evolution of electrical parameters, tracking index and total atrioventricular synchrony. The main confounding factors were first tested in univariate analysis and parameters with an apparent association with the assessed outcome (p-value < 0.10) were selected for analyses in a multivariable model. Categorical parameters derived from continuous numerical variables were determined using receiver operating characteristic (ROC) curves analyses to obtain accurate cutoff values. Logistic regression was performed to identify the factors independently associated with peri-operative complications. A Cox proportional hazard model was used to assess the factors independently associated with long-term mortality and high atrio-ventricular synchrony. Survival curves were calculated using the Kaplan-Meier method. A two-tailed p-value < 0.05 was considered significant.

RESULTS

Baseline characteristics

400 consecutive Micra implantation attempts from July 2015 to May 2022 were included, with 328 first generation Micra (Micra VR, 82%) and 72 second generation Micra (Micra AV, 18%), with a median follow-up of 420 days (14 months) ranging from one day to 80 months.

Baseline characteristics are displayed in **Table 1.**

Most patients were male (n = 228, 57%) with a mean age of 77 years (± 12 years).

Most common comorbidities were atrial fibrillation (62% of all patients), chronic renal failure (50% of all patients) and heart failure (43% of all patients), mostly due to ischemic heart disease.

Patients implanted with Micra AV had significantly less atrial fibrillation (32% vs 68%; $p < 0.001$), less anticoagulant agents (33% vs 66%; $p < 0.001$) but had more frequent history of cancer (46% vs 27%; $p = 0.001$), more antiplatelet agent (36% vs 21%, $p = 0.01$), and more frequent atrioventricular block (100% vs 84%, $p < 0.001$). Patients implanted with Micra AV were also more likely to have diabetes mellitus (42% vs 30%, $p = 0.049$).

The two groups were comparable for all the other studied parameters.

In patients implanted with Micra AV, 14 patients (19%) had a history of heart surgery. Thirty-four patients (47%) had been evaluated with echocardiography to assess mitral inflow with E/A ratio measurement.

Implantation characteristics and follow-up

Implantation characteristics are displayed in **Table 2**.

Micra implantation was successful in 398 patients (99.5%), with no significant difference between the two groups.

Median length of hospitalization following Micra implantation was 1 day (0; [0-46]), with no difference between the two groups. A total of 350 out of 400 patients (87.5%) were discharged the day after the procedure.

Mean duration of follow-up was 585 days (median 420 days).

Indications

The main indication for pacing was atrioventricular block with sinus rhythm (n = 154, 38.5%), followed by chronic atrial fibrillation and atrioventricular block, whether it was related to atrioventricular junction ablation or slow conducting atrial fibrillation (n = 149, 37.3%). Other

indications were abnormal findings in electrophysiological study in patients with syncope or conductive disorders following Transcatheter Aortic Valve Implantation (n = 54, 13.5%), sinus dysfunction (n = 24, 6%) and brady-tachy syndrome (n = 19, 4.8%).

Indications for pacing varied significantly between patients implanted with Micra VR or AV. Micra AV patients had significantly more atrioventricular block with sinus rhythm (86.1% vs 28%, $p < 0.001$) and Micra VR patients had significantly more atrial fibrillation and atrioventricular block (44.8% vs 2.8%, $p < 0.001$), sinus dysfunction (7.3% vs 0%, $p = 0.01$) and brady-tachy syndrome (5.8% vs 0%, $p = 0.03$).

Complications

Major peri-operative complications occurred in 14 patients (3.5%), 13 of them in patients implanted in Micra VR and one in a patient implanted in Micra AV.

Vascular complications at the puncture site were the most frequent (8 out of 14), with two of them requiring vascular surgery and one requiring vascular embolization.

Three patients presented with pericardial effusion, one of them requiring a successful percutaneous pericardiocentesis, eventually leading to death the next day consecutive to refractory cardiogenic shock.

One patient presented with cardiac perforation, managed by urgent cardiac surgery, and was discharged alive after 13 days in intensive care unit.

One patient presented with anaphylactic shock secondary to the injection of prophylactic antibiotherapy during the procedure.

Finally, one patient had a major tricuspid valve dysfunction after implantation.

There was no statistically significant predicting factor of peri-operative complications, both in univariate and multivariate analysis **(Table 3**).

The case number was not predictive of peri-operative complication (**Figure 1**).

Long-term Outcomes

Death occurred in 116 patients (29%) during follow-up, with approximately 50% of patients alive at 4-year follow-up (**Figure 2**).

Heart failure, ischemic heart disease, atrial fibrillation, chronic renal failure, diabetes mellitus, and the presence of an anticoagulant agent or peri-operative complication were predictors of all-cause mortality in univariate analysis (**Table 4**).

Predictors of all-cause mortality in multivariate analysis included ischemic heart disease, atrial fibrillation, and the presence of an anticoagulant agent or peri-operative complications.

Pacemaker syndrome occurred in 6 patients, all implanted with Micra VR, with no significant difference between the two groups (1.8% vs 0%, p = 0.60). Two patients were upgraded to a Micra AV, two to a conventional dual-chamber pacemaker, one was set to VVI 50/min leading to clinical improvement, and one was lost to follow-up.

Pacing induced cardiomyopathy also occurred in 6 patients, with no significant difference between the two groups (1.2% vs 2.8%, p = 0.30), leading to upgrading to cardiac resynchronization therapy whether conventional of through left bundle branch area pacing.

Electrical Parameters

Mean acute pacing threshold was 0.56 V and was similar between Micra VR and Micra AV (0.56 V vs 0.58 V; p = 0.40).

Pacing threshold remained stable during follow-up (**Table 5**), with a mean pacing threshold at last follow-up at 0.57 V ± 0.41 V (p = 0.30).

Mean proportion of ventricular pacing was 66% ± 41% and did not differ between the two groups (67% vs 64%, p = 0.62).

Out of 400 patients, 14 presented with persistent pacing threshold elevation over 2 V (3.5%), with no significant difference between the two groups (2.7% vs 4.2%, p = 0.46). Among the three patients in the Micra AV group that presented with this chronic pacing threshold elevation, one underwent implantation of a second Micra after 2 years because of depleted battery, and one underwent left bundle branch area pacing as he also presented with pacing induced cardiomyopathy.

Electrical parameters in Micra AV patients during follow-up are displayed in **Table 6**.

Mean ventricular impedance decreased significantly between discharge and 1 month follow-up (613 Ohms vs 807 Ohms, p < 0.001), and between 1 month follow-up and 6 months follow-up (552 Ohms vs 613 Ohms, p < 0.001), and then remained stable at 12 months and 24 months with no statistically significant difference (**Figure 3)**.

Mean ventricular sensing increased significantly between discharge and 1 month follow-up (12.8 mV vs 12 mV, p = 0.048) and then remained stable during follow-up.

Mean ventricular threshold remained stable during follow-up, with no statistically significant difference.

Atrial Sensing

Mean A4 sensing remained stable during the 6 first months of follow-up, and then decreased significantly between 6 months and 12 months follow-up (1.8 m/s^2 vs 2.7 m/s^2, p = 0.045).

Among the 72 patients implanted with Micra AV, 13 patients (18%) were switched to VVIR setting, 9 of them (12.5%) due to poor mechanical atrial sensing, and 4 of them (5.5%) because of persistent atrial fibrillation.

Median total atrioventricular synchrony at discharge was 77.6% (53.4%; [2.8%-100%]) and significantly improved at 84.1% (23.9%; [2%-100%]) at 1 month follow-up (p = 0.03). Median total atrioventricular synchrony then significantly decreased at 6 months at 76.3% (44%; [0.5%-99.8%]) (p = 0.03) and remained stable at 71.2% at 12 months (24.1%; [49.4%-98.8%]) (p = 0.42). (**Table 7**).

Among all patients implanted with Micra AV, 50 patients (69%) had at least once an evaluation of Am-Vp/Vp and a total ventricular pacing burden over 20%.

Forty patients out of these 50 patients (80%) presented with at least once a tracking index higher than 66%.

The mean tracking index increased significantly between discharge and the first follow-up (72% vs 54%, p = 0.02), and then remained stable during follow-up with no statistical difference (72% at 6 months, p = 0.72; 67% at 12 months, p = 0.2) (**Figure 4**).

At discharge, 38% of patients had a tracking index higher than 66%. This percentage rose to 71% at 1 month, and then decreased at 66% at 6 months and 54% at 12 months.

Predictors of atrioventricular synchrony

Higher age and mitral E/A ratio lower than 1 were both predictors of high atrioventricular synchrony in univariate analysis. Body mass index, heart failure, ischemic heart disease or cardiac surgery were not predictors of low atrioventricular synchrony (**Table 8**).

An E/A ratio lower than 1 was the only predictor of high atrioventricular synchrony in multivariate analysis (OR = 12.8 [1.02 – 161], p = 0.04).

DISCUSSION

Main results

In this retrospective observational study, we report our experience with Micra Transcatheter Pacing System implantations in patients with an indication for permanent pacing. This cohort of 400 patients, consisting of 328 first generation Micra Transcatheter Pacing System (Micra VR) and 72 second generation Micra Transcatheter Pacing System (Micra AV) is to our knowledge the largest single center real-world report of Micra implanted patients.

Leadless pacemaker implantation represents a recent alternative to conventional transvenous pacing systems and is still expanding[29], with data still lacking compared to conventional transvenous pacemakers. The proportion of pacemaker implantations using leadless devices is still low in Europe, partially on account of its price, reimbursement issues and availability in many European countries[30].

In this context, this large single center cohort is of high value to expand our knowledge about the safety, efficacy, and overall long-term becoming of these patients.

Implantation success rate in our cohort was high at 99.5%, with only 3.5% of peri-operative complications. A total of 87.5% of all patients were discharged the day after the procedure. With a median follow-up of 420 days, long-term complications consisting of pacemaker syndrome and pacing induced cardiomyopathy were low at 3%. We found no predictive factor for peri-operative complications.

Indications for pacing differed significantly between patients implanted with Micra VR or Micra AV, but baseline characteristics were similar, and we found no statistically significant difference in the occurrence of complications during follow-up.

Electrical parameters remained stable during follow-up in both Micra VR and Micra AV, with low pacing thresholds inferior to 2V for 96.5% of patients.

Atrioventricular synchrony, assessed by the tracking index, improved significantly during follow-up and forty patients out of fifty with significant ventricular pacing burden presented with high atrioventricular synchrony at least once.

A pre-operative E/A ratio on trans-mitral Doppler lower than 1 was the only predictor of high atrioventricular synchrony in our cohort.

Baseline characteristics and implantation

Patients implanted with Micra AV had similar characteristics to those implanted with Micra VR, except from them presenting with more frequent diabetes mellitus but less cancer history.

Micra AV patients also had less atrial fibrillation and therefore less anticoagulant agent, but more frequent atrioventricular block and more frequently an antiplatelet agent.

The lower proportion of patients with cancer history in the Micra AV group may be explained by the increased incidence of atrial fibrillation in patients with cancer[31].

The higher proportion of patients with antiplatelet agent might also be indirectly linked to the proportion of atrial fibrillation. As they present more frequently with atrial fibrillation, patients in the Micra VR group often take anticoagulant agents, which most of the time in stable situations allows the discontinuation of antiplatelet agents for other indications such as ischemic heart disease. On the other hand, patients in the Micra AV group tend to have less atrial fibrillation and therefore pursue their antiplatelet agent when indicated.

As for the diabetes mellitus, there seems to be no explanation to this difference between the two groups, but the difference is barely significant ($p = 0.049$).

The main indication for pacing was atrioventricular block with sinus rhythm, followed by atrial fibrillation with atrioventricular block. In patients implanted with Micra VR, the main indication for pacing was atrial fibrillation with atrioventricular block, while in patients implanted with Micra AV, atrioventricular block with sinus rhythm prevailed. This distribution was expected given the difference between Micra VR and Micra AV, with the added algorithm designed to sense atrial mechanical contraction making it possible to use this device in patients with atrioventricular block and sinus rhythm. On the other hand, Micra VR was already known to be particularly useful in patients with chronic atrial fibrillation and atrioventricular block, who only have the need for ventricular pacing.

Two patients in the Micra AV group presented with paroxysmal atrial fibrillation and atrioventricular block related to atrioventricular junction ablation, as they were considered to have a sinus rhythm most of the time.

In our 400-patient experience, device implantation success rate was extremely high at 99.5%, with only 2 failures having occurred in the first 10 patients. This excellent rate was in line with those found in other registries and multicenter investigational and post-approval studies[9,13,14,27,32].

A total of 87.5% of patients were discharged the day after the procedure, in the same manner as patients implanted with transvenous pacemakers, showing the absence of prolonged hospital stay with this procedure. Patients with longer hospital stays were mostly critically ill patients, or patients who suffered from peri-operative complications.

Complications and long-term outcomes

Peri-operative complications were low, occurring in only 14 patients (3.5%), a rate comparable to those found in multicenter registries and post-approval studies[33].

Most complications were vascular (2%), a rate higher than those found in the literature[33,34]. This may be partly because we chose to adjudicate as a vascular complication any hematoma or active bleeding at puncture site that required an intervention, whether it was surgical (2 patients), an embolization (1 patient), a blood transfusion (3 patients), or simply a prolonged manual compression. This anyway highlights the necessity of systematic vascular ultrasound guidance for the femoral venous puncture, especially considering the large caliber of the introducer (27F).

Pericardial effusions and cardiac perforations were scarce (4 patients, 1%), a rate in line with those found in previous studies[35]. One of them required urgent percutaneous pericardiocentesis and eventually led to death, and another had urgent cardiac surgery and was discharged alive after a prolonged stay in the intensive care unit. This shows the need for fluoroscopic guidance during the procedure to confirm the adequate positioning of the device on the interventricular septum.

Only one major tricuspid valve dysfunction occurred, in a patient who also had had percutaneous lead extraction prior to the Micra implantation for an infection of his previous device.

We reported no device dislodgement, embolization, or device infection despite an active infectious context in 110 out of 400 patients (27.5%).

Device infection is one of the most severe complications in transvenous pacing systems, especially in pacing-dependent patients, when device extraction may be needed, and has been described in Polyzos and al. meta-analysis with a 1.6% rate[5]. Main risk factors for device infection are renal insufficiency, diabetes mellitus, malignancy, heart failure, pre-procedural fever, anticoagulant drug use, skin disorders, post-operative hematoma, reintervention, device replacement or revision, lack of antibiotic prophylaxis and procedure duration[5,6].

Device infection exposes patients to a higher risk of mortality and morbidity and is a source of prolonged stay in the intensive care unit, accounting for considerably higher costs as shown in a nationwide cohort study[7].

The absence of device infection in our cohort, despite 27.5% of patients with an active sepsis at the time of the procedure, is encouraging and consistent with most Micra registries and post-approval studies, that record virtually no device infection[36].

This highlights the benefit of this leadless device, as it can be implanted safely in patients with active sepsis, even in patients who underwent device extraction secondary to device infection. Micra implantation has also been described in patient with active tricuspid endocarditis, with no device infection reported at the end of antibiotherapy[37].

This also supports the possibility to choose leadless pacing over transvenous pacing in patients at very high risk of infection such as hemodialyzed patients or critically ill patients, as it has already been described both safe and efficient in other studies[11,12].

As described in other studies, the small surface area of the device as compared to transvenous leads (546 mm^2 vs 3 500 mm^2) and its tendency for encapsulation might be factors explaining the lower risk of infection. Autopsy description of cardiac changes one year after a leadless cardiac pacemaker implantation showed ongoing unspecific chronic inflammation response around the leadless pacemaker with a deep layer of lymphocytes covered by a capsule of collagenous tissue and no endothelial cells, confirming this tendency for encapsulation[38].

Peri-operative complications did not differ between Micra AV and Micra VR complications. This makes sense as the implantation procedure and device are the same, except for an electronic algorithm embarked in the Micra AV. Though the difference was not statistically significant, there seems to be a tendency towards fewer complications in Micra AV patients. Particularly, the only complication occurring in the Micra AV group was at the puncture site, with yet no cardiac injury. This might be explained by a possible higher risk of cardiac injury in the Micra VR group as they tend to present with more cancer history and therefore potentially more radiotherapy, and by an increasing experience among operators with a debated learning curve.

In conventional transvenous pacemakers, several factors have been identified as predictive of peri-operative complications, such as the number of leads implanted, lower body mass index, age, heart failure, hypertension, renal disease, recent device infection and the use of anticoagulant agent[3,7].

In leadless pacemaker implantation, pericardial effusion is known to be associated with advanced age, female sex, congestive heart failure, non-atrial fibrillation indications, chronic lung disease and Micra repositioning[39].

In our cohort, we found no predictive factor for peri-operative complications. The lack of statistically significant predictive factors may be due to the low number of complications in our cohort.

Surprisingly, the case number was not predictive of peri-operative complications despite the described existence of a learning curve with an impact of operator's experience on both safety

and efficacy outcomes[40]. However, in our cohort, major complications such as cardiac injuries and failures of implantation occurred mainly in the first half of procedures, whereas complications in the latest procedures were mainly at the puncture site.

Among our 400 patients, only 12 presented with pacing related complications, with 6 pacing induced cardiomyopathies and 6 pacemaker syndromes. These complications are not specific to leadless devices. All patients presenting with pacing-induced cardiomyopathy and heart failure were upgraded with a resynchronization system and all patients with pacemaker syndromes were upgraded to either a conventional dual-chamber transvenous pacemaker or a Micra AV. There was no pacemaker syndrome in patients implanted with Micra AV, confirming the supposed theoretical benefit of this device, although pacemaker syndrome rates were already low in Micra VR patients.

116 patients died during follow-up (29%), with only one death adjudicated to the procedure. Multivariate analysis showed that ischemic heart disease, atrial fibrillation, anticoagulant agent use, and peri-operative complication were predictive of all-cause mortality. Concerning atrial fibrillation and anticoagulant agent use, this may be explained by the fact that atrial fibrillation in itself is associated with higher mortality[41] and is in most patients the indication for anticoagulant agent use, with high CHA2DS2VASc scores because of their multiple comorbidities.

Mortality did not differ between the two groups either, with a shorter follow-up in the Micra AV group. We can expect a long-term lower mortality in the Micra AV group given the lower rate of atrial fibrillation, a known risk factor for mortality and morbidity.

This low rate of complications and rather high mortality rate needs to be confronted to those of conventional transvenous pacemakers. A French nationwide matched control study[42] recently compared real-life clinical outcomes with these two techniques, showing that patients implanted with leadless VVI pacemakers had a lower rate of all-cause mortality and cardiovascular death within the 30 days after implantation. This is in line with the low peri-operative complication rate in patients with leadless pacemakers we found in our study. During subsequent follow-up, risk of all-cause death was significantly higher in patients implanted with leadless pacemakers in the unmatched population. However, after propensity score matching, risk of all-cause death, cardiovascular death and infective endocarditis were not statistically different. This highlights the fragility of patients implanted with leadless pacemakers, burdened with multiple comorbidities explaining the high mortality rate unconnected with pacemaker implantation.

Electrical parameters

Electrical performances in our cohort of Micra patients were excellent, with a low acute pacing threshold at 0.56 V, remaining stable during follow-up with only 14 patients (3.5%) with a persistent high pacing threshold over 2 V, a limit above which Micra battery life is greatly reduced[16]. This is consistent with existing registries that also report low pacing thresholds. In Micra AV patients with elevated thresholds at implantation[15], more than 75% of patients with acute pacing thresholds between 1 and 2V had a lower chronic pacing threshold, inferior to 1V, inciting to patience in those patients with intermediate pacing thresholds.

This performance is of utmost importance in our cohort of patients, frequently paced with a mean ventricular pacing burden of 66%, and even sometimes fully pacing-dependent, as a lower pacing threshold allows for longer battery life and thus less system revisions and reinterventions.

Acute and chronic pacing thresholds were comparable between Micra AV and Micra VR patients and remained low, which was expected as the implantation procedure and device fixation did not differ between the two generations of leadless pacemakers.

In Micra AV patients, electrical performance was excellent as pacing threshold remained stable with a mean pacing threshold inferior to 1V. Ventricular impedance decreased rapidly after implantation and then remained stable, and ventricular sensing remained stable over 10 mV.

These excellent electrical parameters are in line with previous data in Micra VR patients, as was expected.

Atrial sensing and atrioventricular synchrony

Atrioventricular synchrony in paced patients has shown some benefits both physiological and clinical, despite proving no difference on mortality or morbidity. However, given the amelioration on the quality of life it provides, dual chamber pacing is generally recommended in patients requiring pacemaker implantation. The goal of second generation Micra is to improve said atrioventricular synchrony.

In the MARVEL 2 Study, atrioventricular synchrony in Micra AV patients has been assessed by the sum of Am-Vs, Am-Vp and AV conduction mode switch percentage. Atrioventricular synchrony was achieved if a sensed or paced ventricular beat occurred within the 300 ms following a surface ECG confirmed P wave. In this study, atrioventricular synchrony increased from 27% to 89% when switching from VVI to VDD, meaning that VVI patients in complete atrioventricular block had a 27% random atrioventricular synchrony.

In our study, total atrioventricular synchrony increased significantly between discharge and 1 month to reach a median AV synchrony of 84.1%. Overall, atrioventricular synchrony was excellent with a median AV synchrony over 70% during all follow-up, a ratio considered in Micra AV registries and post-approval studies to mean high atrioventricular synchrony.

However, Arps and al.[43] in their single-center cohort from Duke University in North Carolina achieved higher atrioventricular synchrony during their follow-up with a median AV synchrony at 89% at first follow-up at 2 months and 93% at second follow-up. Baseline population characteristics were comparable to our cohort, except for a more advanced age in our cohort.

This may be explained by a much lower pacing burden in their cohort, with a 10% median pacing burden and 66% of their patients paced less than 50% of the time. In comparison, the median pacing burden in our cohort one month after implantation was 91.5% and remained over 90% during follow-up. This difference in pacing burden may be explained by a higher proportion of paroxysmal atrioventricular block in their cohort, as well as some implantations for sinus node dysfunction (16%), sinus arrest (10%) or tachy-brady syndrome (6%) consisting of patients with no atrioventricular conductive disorder. As a less paced population, their cohort tends to have a higher total atrioventricular synchrony, but this might be mostly from preserved atrioventricular conduction, unlike in our patients who all presented with some form of atrioventricular block.

More recently, Chinitz and al[44] in the AccelAV study and its AccelAV Optimize sub-study evaluated total AV synchrony in the same manner, at rest and then with 24-hours Holter ECG monitoring to confirm AV synchrony in 54 patients with complete atrioventricular block and sinus rhythm. Median AV synchrony at rest in this cohort was 90%, with 85% of patients achieving over 70% AV synchrony. Ambulatory patients had a median AV synchrony at 75% after one month, improving to 85% at 3 months after optimized programming. These results are close to our findings, in a more comparable population of patients with atrioventricular block and sinus rhythm. In this study, cardiac output also improved when switching from VDI to VDD, confirming previous results in transvenous pacemakers.

The influence of the Micra AV algorithm on atrioventricular synchrony was also studied in our Micra AV patients with a ventricular pacing burden over 20% by evaluation of their tracking index. We chose this 20% limit as it has been shown that the risk of pacing induced cardiomyopathy is significantly higher in patients with ventricular pacing higher than 20%[45-50], making it a significant pacing burden. Atrioventricular synchrony in patients paced less than 20% of the time did not seem of clinical relevance. This tracking index, consisting of the ratio

of paced beats tracking an atrial mechanical contraction (Am-Vp) over the total ventricular pacing burden was also evaluated by Arps and al. in their aforementioned cohort.

The percentage of synchronous contraction required to maintain the clinical benefit of AV synchronization over time is unknown but is probably not 100% as previous reports in transvenous pacemakers have shown a minimal clinical impact of intermittent atrial undersensing in patients implanted with conventional transvenous VDD pacemakers[51-52]. In our cohort, we arbitrarily considered that a high ratio of atrioventricular synchrony was achieved if more than 66% of paced QRS were triggered by the sensing of atrial mechanical contraction by the device.

This index appears to be the most significant index to evaluate the impact of Micra AV programming on atrioventricular synchrony, as it eliminates spontaneous atrioventricular conduction and focuses on the role of the pacemaker in maintaining atrioventricular synchrony when pacing is needed.

In our study, 80% of patients with a pacing burden over 20% had a tracking index higher than 66% at least once in their follow-up. Mean tracking index significantly improved between the first evaluation at discharge and the second evaluation at 1 month from 54% to 72%, and then remained stable with no statistical difference for the rest of the follow-up, still over the 66% barrier we chose to establish.

The proportion of patients with a tracking index over 66% was high (71% at one month), and the fact that a tracking index was obtainable in 80% of our patients support the feasibility and efficacy of Micra AV programming strategy to improve atrioventricular synchrony.

These findings are hard to compare to those of the feasibility and post-approval registries of Micra AV, as they did not evaluate this tracking index. Arps and al. reported the only other evaluation of this tracking index we found, with a lower mean tracking index in their cohort at 45% at the first visit and 54% at the second visit. This index was higher in patients with pacing higher than 50% (59% at the first visit, 70% at the second visit), with values comparable to those in our more frequently paced cohort. The reproducibility of these results in patients with high pacing burden is encouraging to support the efficacy of the Micra AV algorithm.

The main key for improving AV synchrony in patients implanted with Micra AV lies in the programming strategy. As it is a recent advance in technology, data on the best programming strategy of Micra AV is still lacking, and many of the first pacemaker settings were at physician's discretion, with no clear guidelines until recently.

Neugebauer and al.[53] provided a thorough analysis of pacemaker programming adjustments affecting atrioventricular synchrony in a real-world. Atrioventricular synchrony in their study

was assessed by the proportion of QRS complexes preceded by a P wave within 300 ms using Holter electrocardiographic recordings. Tracking index was not evaluated. In their study, atrioventricular synchrony was lower when patients had sinus rates higher than 80/min. Atrioventricular synchrony could be improved through stepwise programming, often requiring multiple reprogramming.

A shorter maximum A3 window end, a lower A3 threshold and minimum A4 threshold were shown to improve atrioventricular synchrony. The authors also recommended being careful with AV conduction mode switch, as it assumes intact atrioventricular conduction in case of ventricular rates superior to 40/min, switching to VVI 40/min, which may decrease atrioventricular synchrony in case of 2:1 atrioventricular block or faster ventricular escape rhythm.

While in our cohort mean tracking index improved between discharge and the first visit and then remained stable, Arps and al., Neugebeauer and al. and Chinitz and al. all reported consistent ameliorations in either tracking index or total atrioventricular synchrony at each follow-up, encouraging multiple reprogramming to improve atrioventricular synchrony. This need for multiple reprogramming is discordant with the findings in our cohort, where atrioventricular synchrony did not significantly improve after the first reprogramming. However, the definition of atrioventricular synchrony was often different, and clear guidelines by Medtronic have only been issued recently to standardize the programming strategy. Most of the pacemaker controls in our cohort were done before those guidelines. It is possible that using these guidelines, atrioventricular synchrony may be improved with each reprogramming unlike what we found so far.

This anyway highlights the necessity to have the device at least once programmed by a trained cardiac electrophysiology physician, especially considering the proportion of patients presenting with atrioventricular block. Atrioventricular block is often associated with reactional sinus tachycardia, making maintenance of atrioventricular synchrony difficult because of superposition of accelerometer signals at these high sinus rates. After the first programming, if atrioventricular synchrony remains low, the probability for it to increase with different settings seems low according to our findings but may be helped by standardized guidelines for programming strategy.

Guidelines issued by Medtronic on the basis of expert consensus recommend activating auto A3 window end, auto A4 threshold and turn off the auto A3 threshold to set it manually 1.0 to 1.5 m/s^2 higher than an isolated A3 signal. Rate smoothing can be adapted to sinus rates, and tracking check should be turned off as it may disrupt tracking at high sinus rates. AV conduction

mode switch can be enabled in patients with AV intermittent block after assessing whether the patient has 2:1 atrioventricular block or an idioventricular rhythm. Activity mode may be turned off in patients with intermittent atrioventricular block in the absence of sinus dysfunction.

Predictors of atrioventricular synchrony

We found that advanced age (> 75 years) and a mitral E/A ratio lower than one were the only predictors of high atrioventricular synchrony in univariate analysis. In multivariate analysis, a mitral E/A ratio lower than one was the only predictor of high atrioventricular synchrony.

This reflects the physiology of cardiac filling underlying both the E/A ratio and the Micra AV algorithm. A3 signal as well as E-wave on the mitral inflow reflect passive ventricular filling, and A4 signal and A-wave represent the atrial kick. Therefore, lower E/A ratio means that A4 signal will be proportionally higher than A3 just as the A-wave gets higher than the E-wave.

This explains the better atrioventricular synchrony in older patients, as they tend to have more type 1 mitral inflow, with E/A ratio lower than 1.

Our echocardiographic findings need however to been analyzed with caution, as only 47% of our patients had pre-operative E/A ratio evaluation.

Kowlgi and al[54] found that high atrial synchronous ventricular pacing was associated with smaller body indices, lower proportion of congestive heart failure and prior cardiac surgery. On the other hand, low atrial synchronous ventricular pacing was likely due to small A4-wave amplitude, high ventricular pacing burden and inadequate device reprogramming.

Congestive heart failure is a factor raising the E/A ratio (higher E-wave), and therefore handicaps atrioventricular synchrony as we found in our study. However, prior cardiac surgery in our study was not a predictor of high atrioventricular synchrony, and even seemed pejorative as it altered mechanical atrial contraction. Although there was no statistically significant association, one patient in our cohort underwent cardiac surgery several months after Micra AV implantation and in her case atrioventricular synchrony decreased with a smaller A4-wave amplitude requiring a mode switch to VVI after the cardiac surgery.

In the MARVEL 2 Study, the amplitude of the A4 signal correlated with the echocardiographic parameters E/A, atrial contraction excursion and atrial strain, the two latter being markers of atrial contraction strength[55]. Coronary artery bypass graft also had a negative relationship with A4 amplitude, possibly related to severity of ischemic disease and right atrial cannulation during surgery, both potentially leading to a reduction in atrial contraction as left atrial geometry and pump function is frequent and appears early in ischemic disease[56].

Though other studies may be needed to determine predicting factors for high atrioventricular synchrony, this highlights the importance of pre-operative clinical and echocardiographic evaluation in patients in which Micra AV implantation is considered, as it could rule-out patients who would not benefit from such a technology. The echocardiographic assessment is already recommended in Medtronic guidelines, and patients with E/A higher than 1.5 were excluded from post-approval registries, but the application of this recommendation in a real-world setting may deserve to be systematized.

Limitations

We acknowledge several limitations to our work. The main limitation of our study is inherent to its retrospective observational nature, prohibiting any conclusion for causality. The absence of randomization in this context leaves a risk of residual confounding factors and biased associations. There was missing data regarding baseline characteristics, acute and chronic thresholds, and some patients were lost to follow-up or did not respond to our calls. In Micra AV patients, there was missing data regarding electrical parameters with only a portion of patients included in the Micra AV Study with complete pacemaker interrogations available, and therefore data on electrical parameters should be interpreted with caution. Atrioventricular synchrony was only evaluated through the reports of pacemaker interrogations, with no confirmation using surface ECG or Holter ECG unlike many other studies. Finally, only 47% of Micra AV patients had pre-operative echocardiographic assessment of the E/A ratio available. This may be explained by an intensive care unit setting for most patients, without standardized echocardiographic reports, but also by the notion of high-volume center with patients referred for Micra AV implantation by peripheral centers with echocardiographic evaluation already performed but without standardized reports.

CONCLUSION

Micra implantation in our center is a rapidly growing procedure, with satisfying results in this 400-patient cohort. High implantation success rate, low peri-operative and long-term complication rates, excellent and stable electrical parameters confirm this represents a safe and feasible alternative to conventional transvenous pacing in selected high-risk patients. The emergence of a second generation of leadless pacemakers aiming to track mechanical atrial contraction to achieve atrioventricular synchrony, with an identical implantation procedure, is promising, with results highlighting its safety, feasibility, and efficacy in improving atrioventricular synchrony over time during follow-up. Careful pre-operative assessment is essential to select patients who may benefit from this technology.

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TABLES

Table 1. Patients' characteristics at admission.

	ALL (N=400)	**VR** (N=328)	**AV** (N=72)	**p**
Age (years)	77 ±12	77 ±13	77 ±8	0.61
Male gender (%)	228 (57)	196 (60)	42 (58)	0.93
Body mass index ($kg.m^{-2}$)	28 ±6	28 ±6	28 ±6	0.65
Heart failure (%)	170 (43)	140 (43)	30 (42)	0.65
Ischemic heart disease (%)	93 (23)	79 (24)	14 (19)	0.49
Atrial fibrillation (%)	247 (62)	224 (68)	23 (32)	*<0.001*
Chronic renal failure (%)	199 (50)	163 (50)	36 (50)	1
Chronic pulmonary disease (%)	79 (20)	69 (21)	10 (14)	0.23
Diabetes mellitus (%)	128 (32)	98 (30)	30 (42)	*0.049*
Cancer (%)	120 (30)	87 (27)	33 (46)	*0.001*
Infection (%)	110 (28)	87 (27)	23 (32)	0.35
Antiplatelet agent (%)	95 (24)	69 (21)	26 (36)	*0.01*
Anticoagulation agent (%)	239 (60)	215 (66)	24 (33)	*<0.001*
AV block (%)	346 (87)	274 (84)	72 (100)	*<0.001*

Table 2. Implantation characteristics.

	ALL (N=400)	**VR** (N=328)	**AV** (N=72)	**p**
Pacing indication				
AV block and sinus rhythm (%)	154 (38.5)	92 (28)	62 (86.1)	< 0.001
Paroxysmal	39	25	14	
Chronic	115	67	48	
Sinus dysfunction (%)	24 (6)	24 (7.3)	0	0.01
Paroxysmal	11	11	0	
Chronic	13	13	0	
Brady/Tachy syndrome (%)	19 (4.8)	19 (5.8)	0	0.03
AV block and chronic AF (%)	149 (37.3)	147 (44.8)	2 (2.8)	< 0.001
AV junction ablation	65	63	2	
Slow conducting / Complete AV block	84	84	0	
Abnormal EP study (%)	54 (13.5)	46 (14)	8 (11.1)	0.57
Syncope + long HV interval	30	28	2	
Syncope + carotid sinus hypersensitivity	2	2	0	
Post-TAVI + long HV interval	22	16	6	
Implantation success (%)	398 (99.5)	326 (99.4)	72 (100)	1
Acute pacing threshold (V)	0.56 ± 0.34	0.56 ± 0.32	0.58 ±0.44	0.40
Peri-operative complications (%)	14 (3.5)	13 (4)	1 (1.4)	0.48
Cardiac effusion (%)	3 (0.8)	2 (0.6)	1 (1.4)	0.45
Cardiac perforation (%)	1 (0.2)	1 (0.3)	0	1
Vascular complications (%)	8 (2)	8 (2.4)	0	0.36
Anaphylactic shock (%)	1 (0.2)	1 (0.3)	0	1
Tricuspid valve dysfunction (%)	1 (0.2)	1 (0.3)	0	1
Device infection (%)	0	0	0	1
Pulmonary embolism (%)	0	0	0	1

Table 3. Predictors of peri-operative (≤30 days) complications (N=400).

	UNIVARIATE		MULTIVARIATE	
	OR [95% CI]	p	OR [95% CI]	p
Age (years)*	0.99 [0.95-1.04]	0.77		
Male gender	0.51 [0.17-1.49]	0.22		
Body mass index ($kg.m^{-2}$)*	1.04 [0.97-1.12]	0.29		
Heart failure	1.84 [0.63-5.42]	0.26		
Ischemic heart disease	0.56 [0.12-2.53]	0.42		
Atrial fibrillation	1.12 [0.37-3.40]	0.84		
Infection	0.71 [0.19-2.60]	0.60		
Chronic renal failure	0.55 [0.18-1.67]	0.28		
Chronic pulmonary disease	0.67 [0.15-3.05]	0.59		
Diabetes mellitus	2.18 [0.75-6.36]	0.16		
Cancer	1.31 [0.43-3.99]	0.64		
Antiplatelet agent	0.87 [0.24-3.19]	0.83		
Anticoagulation agent	1.71 [0.53-5.56]	0.35		
Case number (N)*	1.00 [0.99-1.00]	0.21		

* OR, odds ratio, per 1-unit increase for continuous variables.

Table 4. Predictors of all-cause mortality (N=400).

	UNIVARIATE		MULTIVARIATE	
	HR [95% CI]	p	HR [95% CI]	p
Age (years)*	1.01 [0.99-1.03]	0.37		
Male gender	1.36 [0.92-2.00]	0.12	1.28 [0.84-1.95]	0.25
Body mass index ($kg.m^{-2}$)*	1.01 [0.98-1.04]	0.52		
Heart failure	1.53 [1.06-2.20]	*0.02*	1.34 [0.90-1.99]	0.15
Ischemic heart disease	1.95 [1.32-2.89]	*0.001*	1.65 [1.09-2.50]	*0.02*
Atrial fibrillation	1.93 [1.26-2.96]	*0.001*	4.20 [1.75-10.1]	*0.001*
Infection	1.42 [0.93-2.16]	0.11	1.48 [0.94-2.31]	0.09
Chronic renal failure	1.56 [1.07-2.26]	*0.02*	1.40 [0.93-2.11]	0.11
Chronic pulmonary disease	1.47 [0.97-2.22]	0.08	1.36 [0.89-2.09]	0.16
Diabetes mellitus	1.49 [1.02-2.18]	*0.04*	1.25 [0.84-1.86]	0.28
Cancer	1.31 [0.88-1.94]	0.18		
Anticoagulant agent	1.54 [1.03-2.29]	*0.03*	0.42 [0.19-0.96]	*0.04*
Antiplatelet agent	0.90 [0.57-1.41]	0.64		
Peri-operative complication	2.99 [1.46-6.14]	*0.01*	3.39 [1.58-7.26]	*0.002*
Ventricular pacing ≥20%	1.37 [0.82-2.28]	0.23		
Case number (N)*	1.00 [1.00-1.00]	0.79		

* OR, odds ratio, per 1-unit increase for continuous variables.

Table 5. Follow-up.

	ALL (N=400)	**VR** (N=328)	**AV** (N=72)	**p**
Chronic complications (%)	26 (6.5)	19 (5.8)	5 (6.9)	0.78
Chronic threshold elevation (>2V) (%)	14 (3.5)	9 (2.7)	3 (4.2)	0.46
Pacemaker syndrome (%)	6 (1.5)	6 (1.8)	0	0.60
Pacing induced cardiomyopathy (%)	6 (1.5)	4 (1.2)	2 (2.8)	0.30
Mean proportion of ventricular pacing (%)	66 ± 41	67 ± 41	64 ± 41	0.62
Chronic pacing threshold (V)	0.57 ± 0.41	0.56 ± 0.38	0.60 ± 0.52	-

Table 6. Evolution of electrical parameters in Micra AV patients over time.

	Discharge	1 month	6 months	12 months	24 months
Ventricular impedance					
Number of patients	64	68	40	22	5
Mean ventricular	807	613	552	528	556
impedance (Ohms)	± 193	± 104	± 84	± 131	± 86
p	-	< 0.001	< 0.001	0.24	0.55
Ventricular sensing					
Number of patients	52	66	38	18	3
Mean ventricular	12	12.8	13.2	12.4	10.6
sensing (mV)	± 5.1	± 4.9	± 5	± 4.8	± 5.7
p	-	0.048	0.4	0.11	0.94
Ventricular threshold					
Number of patients	67	68	41	22	5
Mean ventricular	0.58	0.6	0.72	0.67	0.98
threshold (V)	± 0.4	± 0.5	± 0.7	± 0.5	± 1.1
p	-	0.34	0.64	0.44	0.39
A4 sensing					
Number of patients	9	45	28	16	5
Mean A4 sensing (m/s^2)	1.6 ± 1.8	2.6 ± 1.9	2.7 ± 1.9	1.8 ± 1.6	2.4 ± 0.5
p	-	0.86	0.66	0.045	0.89

Table 7. Evolution of total atrioventricular synchrony in Micra AV patients over time.

	Discharge	**1 month**	**6 months**	**12 months**
Number of patients	49	60	37	14
Median pacing burden (%)	93.4 (81.8 ; [0.2-100)	91.5 (59.7 ; [0.2-100]	96.8 (45.4 ; [1-100])	99.6 (0.3 ; [99.4-100])
Median AV synchrony (%)	77.6 (53.4 ; [2.8 -100])	84.1 (23.9 ; [2 -100])	76.3 (44 ; [0.5 -99.8])	71.2 (24.1 ; [49.4 -98.8])
p	-	0.03	0.03	0.42

Table 8. Predictors of Am-Vp/Vp ≥66% in Micra AV patients with Vp ≥20% (N=40).

	UNIVARIATE		MULTIVARIATE	
	OR [95% CI]	p	OR [95% CI]	p
Age (years)*	1.11 [1.01-1.21]	*0.02*	1.11 [0.97-1.28]	0.10
Male gender	0.71 [0.18-2.84]	0.63		
Body mass index ($kg.m^{-2}$)*	0.97 [0.84-1.12]	0.68		
Heart failure	1.71 [0.41-7.14]	0.46		
Ischemic heart disease	1.19 [0.20-7.23]	0.85		
Atrial fibrillation	0.52 [0.12-2.17]	0.37		
Infection	1.59 [0.34-7.38]	0.55		
Chronic renal failure	1.20 [0.30-4.78]	0.80		
Chronic pulmonary disease	1.19 [0.20-7.23]	0.85		
Diabetes mellitus	1.06 [0.25-4.50]	0.94		
Cancer	0.73 [0.19-2.90]	0.66		
Cardiac surgery	0.36 [0.07-1.81]	0.22		
Mitral E/A <1	19.5 [1.78-214]	*0.004*	12.8 [1.02-161]	*0.04*

* OR, odds ratio, per 1-unit increase for continuous variables.

FIGURES

Figure 1. Cumulative curve of major complications according to case number.

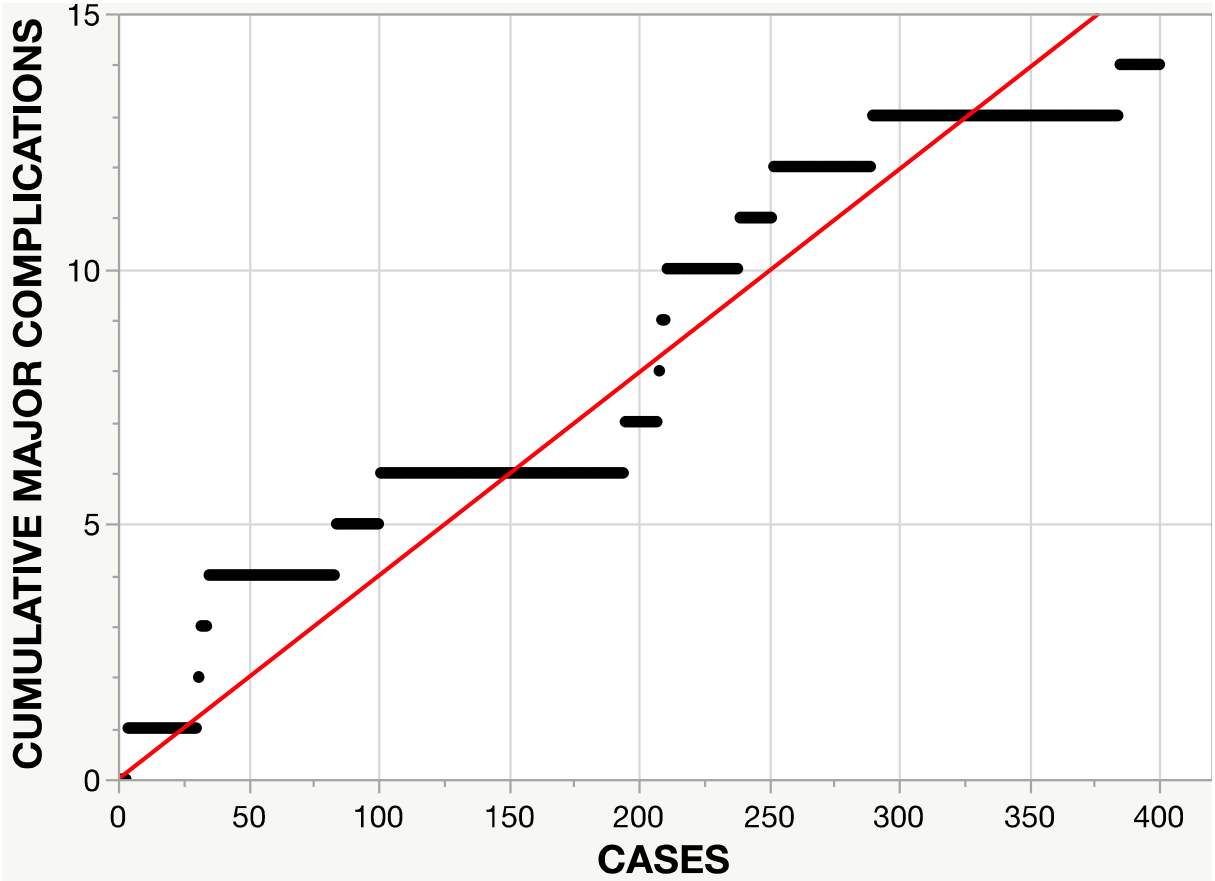


Figure 2. Kaplan-Meier survival curve for all-cause mortality in the overall population.

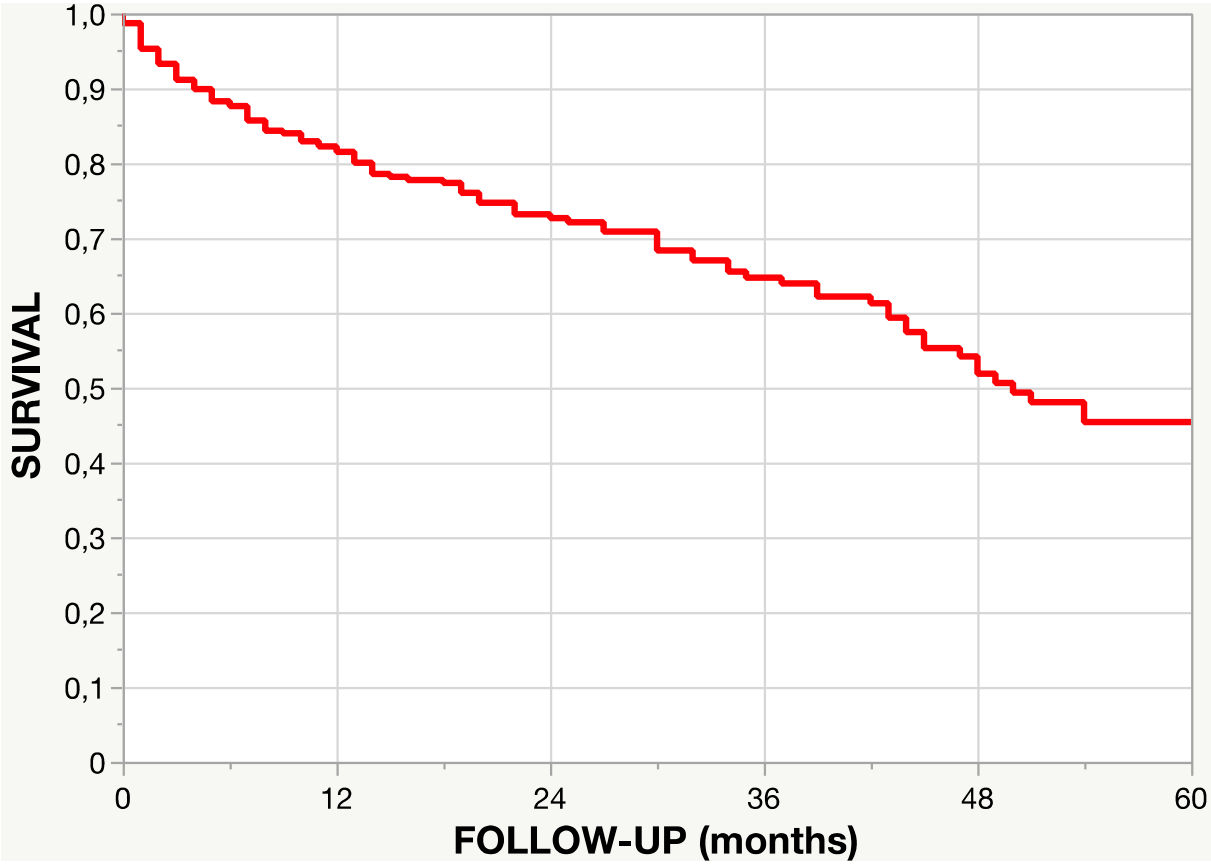
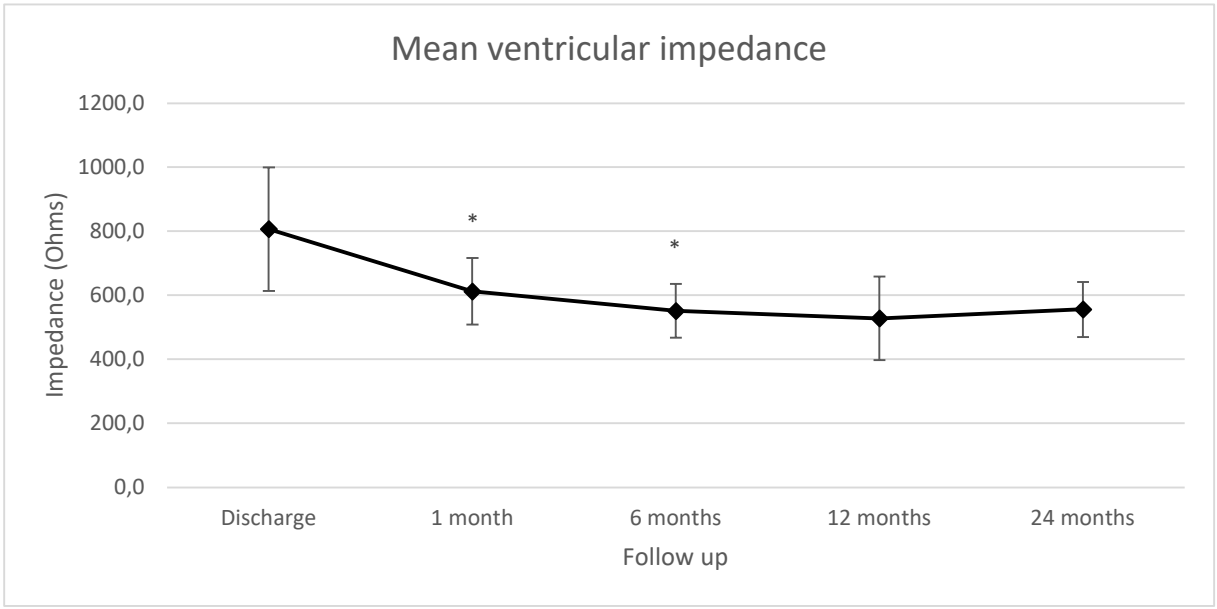


Figure 3. Evolution of electrical parameters in Micra AV patients over time.

3a.



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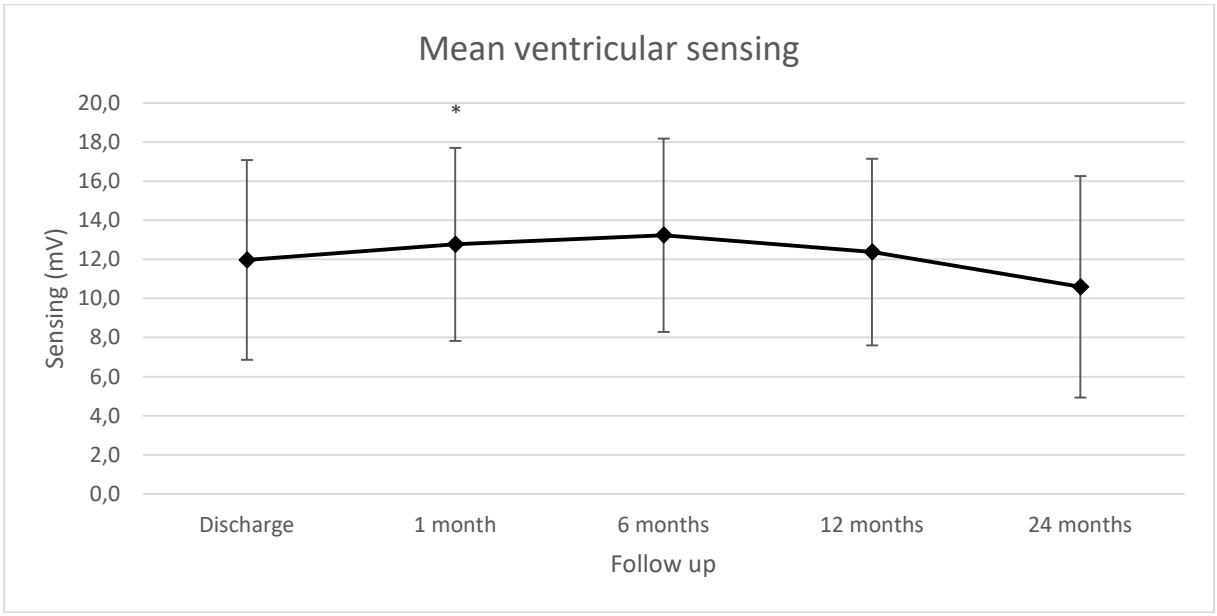

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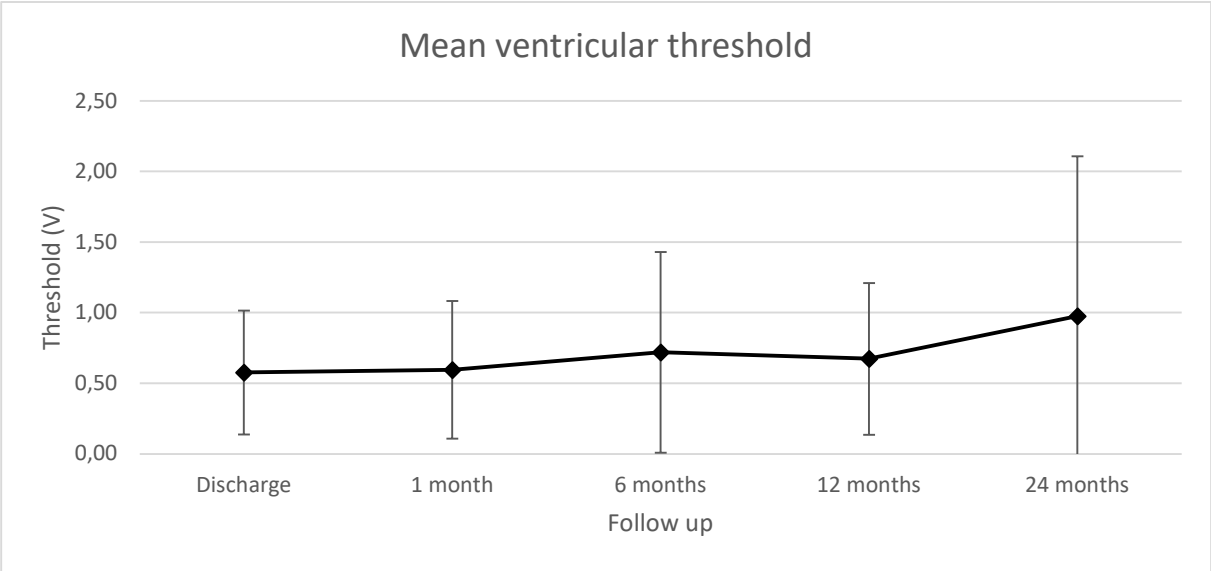

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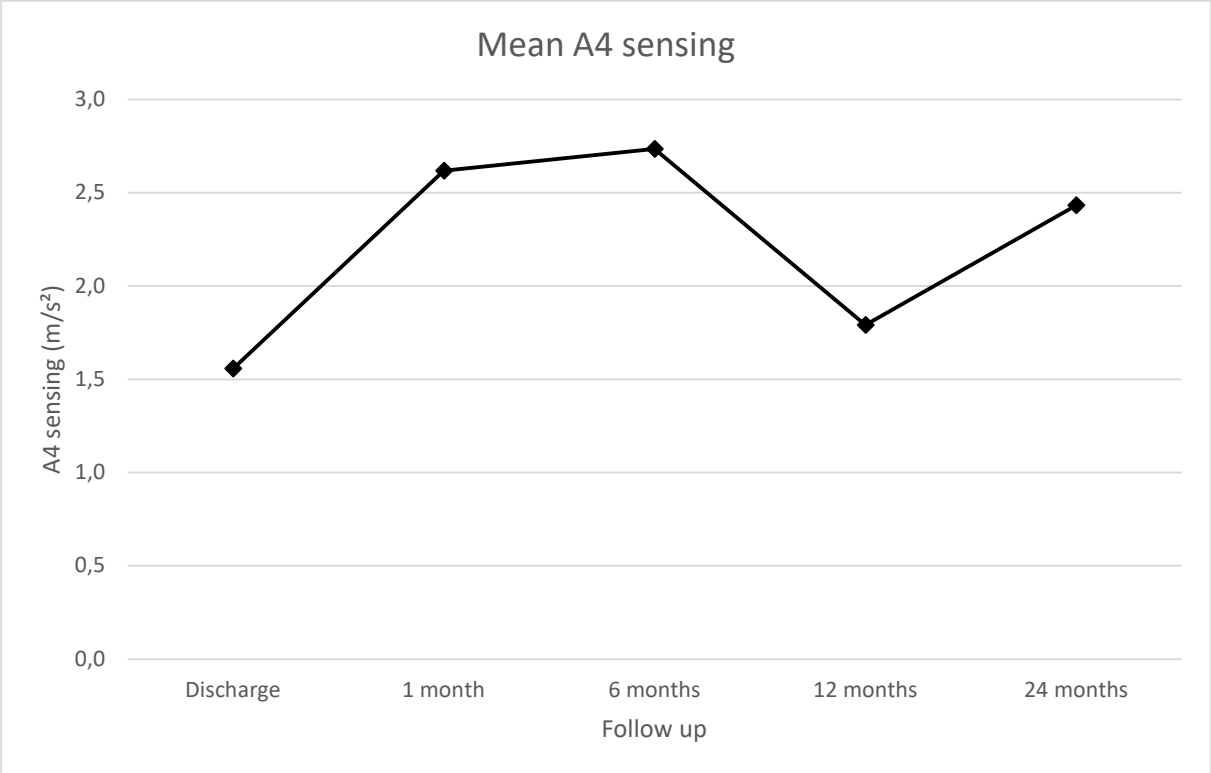
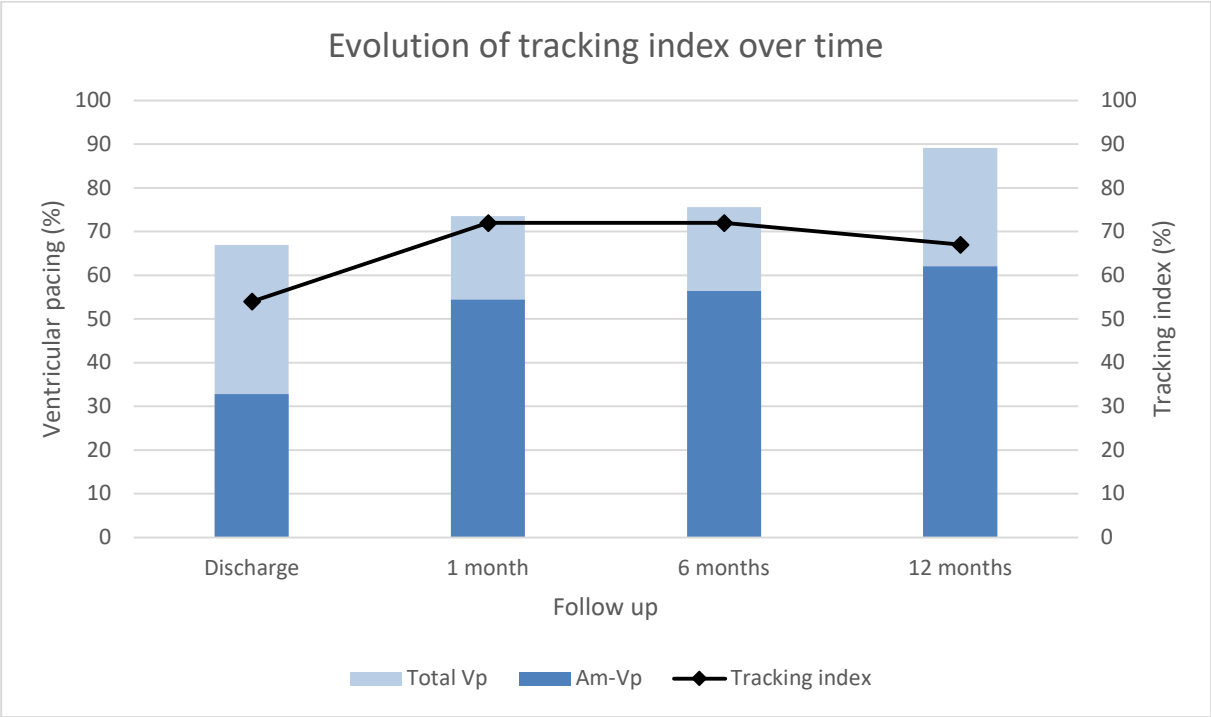


3a. Mean ventricular impedance over time. **3b**. Mean ventricular sensing over time. **3c**. Mean ventricular threshold over time. **3d**. Mean A4 sensing over time.

Bars represent standard deviation from mean value.

***** indicates a statistically significant difference compared to the previous value ($p < 0.05$).

Figure 4. Evolution of tracking index over time.



Vu, le Directeur de Thèse

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LENORMAND Thibault
58 Pages – 8 tableaux – 4 figures

Résumé :

Introduction : L'efficacité et la sécurité de la stimulation cardiaque sans sonde comme alternative aux pacemakers conventionnels a été montrée, avec une évolution récente par l'ajout d'algorithmes permettant une synchronisation atrio-ventriculaire. L'objectif de l'étude était de rapporter l'expérience avec ces deux générations de pacemakers sans sonde dans un centre à haut volume d'implantation.

Méthodes : Cette étude observationnelle rétrospective a inclus les 400 premiers patients ayant bénéficié de l'implantation d'un stimulateur cardiaque sans sonde au CHRU de Tours depuis 2015. Les évènements évalués au cours du suivi étaient les complications et les paramètres électriques, en comparant les pacemakers sans sonde de première (Micra VR) et de seconde génération (Micra AV). La synchronisation atrio-ventriculaire a été évaluée chez les patients porteurs d'un Micra AV. Le recueil des données s'est fait par consultation des dossiers médicaux.

Résultats : Parmi les 400 procédures, on recensait 328 Micra VR et 72 Micra AV. Le taux de succès d'implantation était de 99.5%. 87.5% des patients étaient sortis de l'hôpital le lendemain de l'intervention. Le seuil de stimulation est resté stable et inférieur à 2 V chez 96.5% des patients. Le taux de complications péri-opératoires était de 3.5%. Le suivi était comparable entre les deux groupes. Parmi les Micra AV, la synchronisation atrio-ventriculaire s'améliorait significativement entre la sortie et la première visite (indice de suivi 72% vs 54%, p = 0.02) et 40 patients sur les 50 avec une stimulation ventriculaire significative ont présenté une bonne synchronisation atrio-ventriculaire (> 66%). Un ratio E/A sur le flux Doppler trans-mitral en échocardiographie inférieur à 1 en préopératoire était le seul prédicteur d'une bonne synchronisation atrio-ventriculaire en analyse multivariée (p = 0.04).

Conclusion : La stimulation cardiaque sans sonde est une alternative efficace et sûre à la stimulation cardiaque conventionnelle. L'apparition d'un algorithme de synchronisation atrio-ventriculaire permet un élargissement des indications d'implantation pour les stimulateurs cardiaques sans sonde.

Mots-clés : stimulation cardiaque sans sonde, complications péri-opératoires, synchronisation atrioventriculaire

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