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Thèse préparée sous la direction du **Professeur Haran Burri**

" Stimulation sans sonde avec le système de stimulation cardiaque transcathéter Micra® en pratique : Expérience initiale en suisse romande "

Thèse
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DOCTORAT EN MEDECINE

Thèse de :

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Intitulée :

Stimulation sans sonde avec le système de stimulation cardiaque transcathéter Micra® en pratique : expérience initiale en Suisse Romande

La Faculté de médecine, sur le préavis du Comité directeur des thèses, autorise l'impression de la présente thèse, sans prétendre par-là émettre d'opinion sur les propositions qui y sont énoncées.

Genève, le 26 novembre 2020

Thèse n° **11027**

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Doyen

N.B. - La thèse doit porter la déclaration précédente et remplir les conditions énumérées dans les "Informations relatives à la présentation des thèses de doctorat à l'Université de Genève".

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Résumé

La stimulation cardiaque est le traitement classique des bradycardies. Des complications liées à cette technique sont rapportées chez 5 à 10% des patients. Un nouveau dispositif sans sonde (TCLP) développé en 2015 permet de diminuer certaines complications. Les études expérimentales sur l'implémentation de ce nouveau stimulateur cardiaque montrent des taux de complications plus faible (2-5%) qu'avec les appareils traditionnels. Cette étude rétrospective incluant 97 patients rapporte l'expérience Suisse romande sur l'introduction en pratique clinique du TCLP. Nos résultats montrent une implantation avec succès et des paramètres électriques comparables avec les études expérimentales. Notre taux de complications majeures péri-interventionnelles et dans le suivi est plus élevé (9.8%). Cette différence s'explique par une population âgée avec plus de comorbidités ainsi qu'une courbe d'apprentissage des opérateurs. Le TCLP est une technologie attrayante pour certains patients présentant des contre-indications à l'implantation d'un stimulateur classique. Comme toute nouvelle technologie, une formation rigoureuse des opérateurs est indispensable.

Abréviations

BAV : Bloc atrio-ventriculaire

FA : Fibrillation auriculaire

TCLP : Transcatheter leadless pacemaker = stimulateur cardiaque sans sonde

Introduction

Les troubles du rythme sont des motifs fréquents de consultation en cardiologie. Il peut s'agir de bradycardie, de tachycardie ou de rythme cardiaque irrégulier. Nous discuterons principalement des brady-arythmies dont le traitement est, pour la grande majorité des cas et en absence de cause réversible, l'implantation d'un stimulateur cardiaque permanent ou « pacemaker ». Les dispositifs classiques comprennent un boîtier avec sa batterie ainsi qu'une à deux sondes à destination du ventricule droit, de l'oreillette droite et/ou du faisceau de His. Ces sondes sont introduites via la veine céphalique ou sous-clavière à destination du cœur droit. Le boitier est lui inséré dans une loge sous cutanée à proximité du muscle pectoral. Nous ne parlerons pas ici des dispositifs à trois sondes que sont les thérapies de resynchronisation cardiaque indiquées chez certains patients souffrant d'insuffisance cardiaque sévère

En 2017, 5246 patients ont été implanté d'un stimulateur cardiaque en Suisse (https://www.pacemaker.ch/fr/statistik/default.asp). Les indications les plus fréquentes sont le bloc atrio-ventriculaire (BAV) de 2ème ou 3ème degré, la dysfonction du nœud sinusal et la fibrillation auriculaire (FA) à réponse ventriculaire bradycarde. Les statistiques suisses de 2012 montrent que l'indication la plus fréquente au stimulateur cardiaque est le BAV (43%) suivi de la maladie du nœud sinusal (29.4%) puis de la FA lente (14%).

Il existe d'autres indications plus rares comme le syndrome du sinus carotidien et certaines formes de malaise vasovagal. Avec le vieillissement de la population, ces chiffres vont continuer à augmenter.

Les étiologies des bradycardies sont nombreuses et les causes réversibles doivent être activement recherchées. L'origine peut être intrinsèque au myocarde : dégénérescence des voies de conduction liée à l'âge, cardiopathie ischémique, cardiomyopathie infiltrative ou dilatée, myocardite, endocardite, maladie de Lyme ou Chagas, maladie rhumatologique, post chirurgie cardiaque ou remplacement valvulaire aortique percutané. Il existe également des étiologies de bradycardie extrinsèque comme le réflexe vagal, l'activité physique intense, les médicaments (bétabloquant, anticalcique, bloqueurs des canaux sodiques ou potassiques), les troubles métaboliques ou électrolytiques (1) .

Les symptômes des bradycardies sont aspécifiques et les présentations cliniques sont très variées. Elles comprennent la syncope, les palpitations, les vertiges et les signes d'insuffisance cardiaque comme la dyspnée, l'asthénie et la diminution de capacité fonctionnelle.

Depuis l'implantation en 1958 du premier stimulateur cardiaque par Ake Senning et Rune Elmqvist, des avancées technologiques majeures sont réalisées dans le domaine de la stimulation cardiaque avec notamment la réduction en taille des batteries, le développement des appareils à double chambre puis des thérapies de resynchronisation et plus récemment de la stimulation sélective du faisceau de His. A partir des années 60, les sondes de stimulation intraveineuse endocardique remplacèrent les sondes épicardiques. La batterie au Lithium-iodine développée dans les années 70 a également permis une nette amélioration de la longévité des stimulateurs cardiaques.

Malgré ces prouesses technologiques, l'implantation d'un stimulateur cardiaque reste grevée de certaines complications péri- et post- procédurales

potentiellement graves allant jusqu'à 9-12% à 6 mois selon certaines séries (2, 3). Les complications les plus fréquentes de l'implantation d'un tel dispositif sont à court terme le pneumothorax, l'hématome au niveau de la poche, les douleurs post opératoires, les perforations myocardiques et le déplacement de sonde. Les complications les plus redoutées à moyen et long terme sont les infections de boîtier ou de sondes, la fracture de sonde et les lésions de la valve tricuspide. Certaines de ces complications nécessitent parfois une ablation complète du stimulateur et des sondes.

L'idée d'une stimulation intracavitaire sans sonde avait déjà été expérimentée sur un chien en 1970 mais en raison de la courte durée de vie de la batterie et de la complexité de la fixation, cette technique ne se développa pas d'avantage (4)

Un nouveau type de stimulateur cardiaque sans sonde est apparu sur le marché depuis 2013. Il s'agit d'un dispositif implanté directement dans le ventricule droit qui possède les mêmes propriétés techniques qu'un stimulateur cardiaque traditionnel simple chambre. La première implantation fut réalisée en décembre 2013 aux États-Unis. Le dispositif a reçu la conformité européenne en avril 2015 (CE0123) et été approuvé par la FDA (Food and Drug Administration) en juin 2016. Les premières implantations suisses d'un TCLP datent du 1 juin 2015 aux Hôpitaux Universitaires de Genève (HUG) et à l'hôpital cantonal de Fribourg.

Discussion

Il existe actuellement sur le marché deux types de TCLP ; le Nanostim ™ de St-Jude et le MICRA™ de Medtronic. Nous nous intéresserons principalement au dispositif MICRA™ car c'est le seul actuellement utilisé en Suisse.

Le MICRA™ est un dispositif de 2.0gr, 0.8cm^3 mesurant 25,9mm de longueur et 6.7 mm de diamètre **(image 1).** Comme tout stimulateur cardiaque, il est composé d'une batterie en Lithium, d'une anode à son extrémité proximale et d'une cathode à son extrémité distale. Il permet une détection ainsi qu'une stimulation ventriculaire droite. Le courant électrique généré entre l'anode et la cathode va permettre la dépolarisation des cellules myocardiques adjacentes et induire un battement cardiaque. Ce système est implanté de manière percutanée avec anesthésie locale via un cathéter de 23 French introduit dans la veine fémorale. Le TCLP est, après s'être assuré de sa stabilité et de seuils de stimulation satisfaisants, largué directement dans le ventricule droit où le système de fixation composé de 4 ancres en nitinol va permettre un positionnement sûr et efficace. Le déploiement est réalisé sous contrôle fluoroscopique.

Image 1 : Système de stimulation cardiaque transcathéter MICRA™

Le MICRA™ est donc une alternative au stimulateur simple chambre endoveineux. Son indication la plus fréquente est, comme le stimulateur monocaméral, une FA permanente avec insuffisance chronotrope ou BAV complet. Il n'est pas indiqué pour les autres formes de bradycardies (BAV chez un patient en rythme sinusal, maladie du nœud sinusal) où un stimulateur double chambre est recommandé pour préserver la synchronisation atrio-ventriculaire.

La première étude sur l'expérience clinique avec le MICRA™ est publiée en novembre 2015 par Reynolds et al. (5). Cette étude prospective sans groupe contrôle inclus 725 patients ayant une indication classe I et II selon les recommandations internationales à une stimulation cardiaque monocamérale. Les critères de jugement primaires sont séparés en critère de sécurité et d'efficacité. Le critère de sécurité est une implantation du dispositif sans complication liée à la procédure et le critère d'efficacité est le pourcentage de patient avec un seuil de stimulation bas et stable à 6 mois. Cette étude montre un taux d'implantation avec succès de 99.2 % (719 patients sur 725) avec un taux de complications faible comprenant 28 complications majeurs chez 25 patients (3.4%). Le critère d'efficacité est également très satisfaisant avec 98.3% des patients remplissant les paramètres électriques de stimulation efficace et stable à travers le temps. Ces résultats sont comparés à des cohortes historiques de patients implantés avec des stimulateurs cardiaques classiques et les auteurs concluent que ce nouveau dispositif a un profil de sécurité plus favorable (réduction de 48% de complications) avec une efficacité comparable.

Les complications liées au TLCP dans la publication originale sont majoritairement des lésions myocardiques avec perforation ou épanchement péricardique (5). Les autres complications sont reparties avec des complications liées au point de

ponction, les augmentations de seuil et de manière plus rare des évènements cardio-vasculaire comme infarctus, insuffisance cardiaque ou maladie thombo-embolique.

Malgré le taux de complications plus faible en comparaison avec les cohortes historiques des stimulateurs cardiaques classiques, ces résultats soulèvent des questions sur l'application clinique quotidienne des TLCP. Dans ce contexte, Roberts et al. publient une étude prospective observationnelle multi-centrique avec 795 patients implantés d'un MICRA™. (6) Les résultats confirment le profil sécuritaire satisfaisant du TLCP avec un taux de succès d'implantation de 99.6% et un nombre de complication encore plus faible que dans l'étude de Reynolds avec 13 complications majeurs rapportées (1.51%). Le taux d'épanchement péricardique rapporté est de 0.63% contrairement au 1.6% de l'étude de Reynold et al. Ce registre est encore en cours de recrutement pour des analyses à plus long terme. Ces résultats encourageants permettent à la stimulation sans sonde de poursuivre son utilisation en pratique clinique. Il est important de souligner que ces deux études majeures sont sponsorisées par Medtronic.

A la lumière de ces données, nous avons décidé de nous intéresser à l'expérience Suisse romande de l'implantation des TCLP de type MICRA™. En effet, en pratique clinique, nous avons remarqué que le taux de complications semblait plus élevé que ce qui était rapporté. Il nous paraissait également intéressant de pouvoir analyser en pratique clinique les résultats et performances de cette nouvelle technologie dont les avantages sont nombreux avec cependant des complications potentiellement graves décrites.

Notre travail est une étude rétrospective observationnelle ayant pour but d'évaluer la sécurité et l'efficacité du TCLP de type MICRA™ dans un contexte

clinique quotidien. Le caractère rétrospectif de notre étude permet de s'affranchir du biais de sélection potentiellement présent dans les études prospectives. Nous avons associé les universités de Genève, Lausanne ainsi que les hôpitaux de Fribourg et de Sion pour regrouper toutes les implantations de TCLP entre juin 2015 et juin 2017. Au total, 92 patients sont inclus dans notre registre avec par la suite un travail de récupération des données comme les caractéristiques de base des patients, les indications d'implantation, les complications initiales, les paramètres électriques à l'implantation, le temps de procédure et la durée de fluoroscopie Pour le suivi, nous avons également récupéré tous les paramètres électriques du TCLP lors des contrôles à 1 mois, 6 mois et 12 mois. La survenue de complications cliniques était recherchée sur les consultations de suivi.

Nos résultats montrent que le taux d'implantation avec succès (97.8%) est comparable aux données existantes. Les paramètres électriques de stimulation à l'implantation ainsi que durant le suivi sont également bons et globalement semblables aux résultats déjà publiés.

En revanche, notre taux de complications de 9.8% est nettement plus élevé que dans les études précédemment citées. Il existe plusieurs explications à ces résultats. Il s'agit d'une première expérience dans plusieurs centres avec plusieurs opérateurs. Une phase d'apprentissage pour chaque opérateur peut expliquer la survenue plus fréquente de complications lors d'introduction de nouvelles techniques. Il est important de signaler que la plupart des complications dans notre registre sont survenues durant les premiers cas des opérateurs confirmant l'hypothèse d'une courbe d'apprentissage. Il s'agit effectivement d'une technique radicalement différente de l'implantation d'un stimulateur classique et son apprentissage requiert une formation particulière de la manufacture.

Nos patients étaient globalement plus âgés (81 ans vs 75 ans) et avec plus de comorbidités que ceux des études expérimentales. Ce biais de sélection dans les études de Reynolds et al. et Roberts et al. pourrait en partie expliquer leur taux de complications plus faible. Nous avons enregistré un taux de mortalité non lié au TCLP important allant jusqu'à 20% dans le suivi. Ce taux de mortalité est le reflet d'une population très fragile et donc plus à risque de complications lors de procédures.

La question du retrait du TCLP demeure un sujet encore peu étudié pour lequel il existe peu de données. Bien que les recommandations du fabricant recommandent de laisser le TCLP en place en cas de fin de vie, il existe des situations comme l'infection endovasculaire, les seuils trop élevés à l'implantation ou l'embolisation du TCLP qui nécessitent un retrait. Afzal et al. ont montré que sur 29 retraits, aucune complication majeure n'est survenue avec une extraction possible jusqu'à 95 jours post implantation (7).

Le caractère rétrospectif est une limitation majeure de notre étude avec des complications mineures et majeures possiblement sous diagnostiquées car non reportées dans les dossiers des patients. Certains patients ont été malheureusement perdu de vue durant le suivi.

Pour conclure, la stimulation cardiaque sans sonde miniature est une nouvelle technologie très attrayante permettant de s'affranchir de complications redoutées de la stimulation cardiaque classique comme les endocardites, les déplacements/fractures de sondes ou encore les hématomes sur la poche du pacemaker. La durée de vie du TCLP est similaire à celle d'un boitier classique et

son utilisation est une bonne alternative au stimulateur simple chambre lors de situation spécifique ; par exemple infection active, antécédents de complications liées aux sondes, antécédents d'endocardite, nécessité de préserver un capital veineux, post chirurgie tricuspidienne.

Comme toute nouvelle technologie, nous devons rester prudent lors son implémentation en pratique clinique d'où l'importance de tenir des registres et un suivi des patients implantés par TCLP. L'analyse de ces données nous permettra de progresser parallèlement au progrès technologique avec un maximum de sécurité pour les patients. L'existence d'une courbe d'apprentissage liée à l'opérateur nécessite une formation rigoureuse par la manufacture. Des études randomisées à large échelle comparant un TCLP et un système endoveineux simple chambre classique n'ont pas encore été réalisées raison pour laquelle il n'existe actuellement pas de recommandation forte pour préférer ce système à un stimulateur classique.

Références

1. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J. 2013;34(29):2281-329.
2. Kirkfeldt RE, Johansen JB, Nohr EA, Jørgensen OD, Nielsen JC. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. Eur Heart J. 2014;35(18):1186-94.
3. Udo EO, Zuithoff NP, van Hemel NM, de Cock CC, Hendriks T, Doevendans PA, et al. Incidence and predictors of short- and long-term complications in pacemaker therapy: the FOLLOWPACE study. Heart Rhythm. 2012;9(5):728-35.
4. Spickler JW, Rasor NS, Kezdi P, Misra SN, Robins KE, LeBoeuf C. Totally self-contained intracardiac pacemaker. J Electrocardiol. 1970;3(3-4):325-31.
5. Reynolds D, Duray GZ, Omar R, Soejima K, Neuzil P, Zhang S, et al. A Leadless Intracardiac Transcatheter Pacing System. N Engl J Med. 2016;374(6):533-41.
6. Roberts PR, Clementy N, Al Samadi F, Garweg C, Martinez-Sande JL, Iacopino S, et al. A leadless pacemaker in the real-world setting: The Micra Transcatheter Pacing System Post-Approval Registry. Heart Rhythm. 2017;14(9):1375-9.
7. Afzal MR, Daoud EG, Cunnane R, Mulpuru SK, Koay A, Hussain A, et al. Techniques for successful early retrieval of the Micra transcatheter pacing system: A worldwide experience. Heart Rhythm. 2018;15(6):841-6.

Annexes

1. Article original :

Valiton V, Graf D, Pruvot E, Carroz P, Fromer M, Bisch L et al. *Leadless pacing using the transcatheter pacing system (Micra TPS) in the real world: initial Swiss experience from the Romandie region*. Europace 2019;21:275–80.

ESC European Society of Cardiology

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CLINICAL RESEARCH

Leadless pacing using the transcatheter pacing system (Micra TPS) in the real world: initial Swiss experience from the Romandie region

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Aims Leadless pacemakers are implanted in Switzerland since June 2015. Large worldwide registries have shown high implant success, low complication rates, and good electrical parameters up to 12 months' follow-up. However, data are scarce outside the investigational setting. The purpose of this study is to assess the real-world experience regarding clinical safety and efficacy of Micra TPS (transcatheter pacing system) leadless pacemakers.

Methods and results Retrospective observational, multi-centre study designed to assess initial safety and efficacy of the Micra TPS in the Swiss Romande region. A total of 92 patients were included from four different centres with an implantation success rate of 97.8% (90 of 92). Thresholds were overall low at implantation (median 0.38 V/0.24 ms, ranging from 0.13 to 2.88 V/0.24 ms) and remained stable over 1-year follow-up. The perioperative serious adverse event rate was 6.5% in six patients which lead to prolonged hospitalization in five patients and death in one patient. In addition, three further major events (3.3%) occurred during an average follow-up of 1 year, requiring implantation of a standard transvenous pacemaker in two patients, and surgical explantation of the Micra TPS in one patient due to intractable ventricular tachycardia.

Conclusion Leadless pacemakers are a valuable adjunct for treating selected patients requiring single-chamber pacing. However, in this initial experience, major complication rates were high (9.8%). The implant procedure requires proper training and should be performed in an adequate setting.

Keywords Leadless pacemaker • Transcatheter pacing system • Implantation • Follow-up • Complications

Introduction

Since 1970, totally self-contained intra-cardiac pacemakers were studied but never made it to clinical practice because of battery longevity and size.[1] In June 2015, the Micra TPS (Transcatheter Pacing System, Medtronic, Minneapolis, MN, USA) was introduced in Switzerland. Unlike conventional pacemakers with leads and a subcutaneous pocket, these miniature intra-cardiac devices are implanted directly in the right ventricle. The aim of this new device is to avoid lead and pocket-related complications of traditional pacing systems, which can amount to up to 9–12% of cases at 6 months according to different studies.[2,3]

In the Micra investigational study, Reynolds *et al.* report a 99.2% successful implant rate (719/725 patients).[4] The efficacy endpoint defined by low and stable pacing threshold at 6 months was 98.3% (data from 292 patients). The long-term safety of the same group was consistent with the early published data with a freedom from major complications of 96% at 12 months.[5] In a post-market registry, Roberts *et al.*[6] confirmed the good results of the investigational study, with an

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What's new?

- This real-world experience confirms that Micra TPS implantation has a high procedural success (97.8%), with overall good electrical parameters which remain stable over time.
- The incidence of major complications was however high at close to 10%, most probably explained by the fact that this series reported the operators' initial experience and because of the fragile patient population.
- Per-operative death and intractable monomorphic ventricular tachycardia requiring emergent surgical explantation of the device, are published for the first time.

implant success rate of 99.6%, a low rate of major complications at 30 days (1.5%), and excellent electrical performance of the Micra TPS.

As this is new technology and there is currently only one study in the real-world setting, our aim was to assess the performance and safety of this device in the Romandie (French-speaking) region of Switzerland.

Methods

Study design

The study is retrospective, observational, non-randomized, multicentric, and designed to evaluate the early performance and safety of the Micra TPS in the Romandie region. The study plan protocol was approved by the institution ethics committee of the University Hospital of Geneva, which served as the central committee for the study centres.

Patients, procedure, and study device

All patients intended to be implanted with a Micra TPS from June 2015 to May 2017 were included in the study. Patients had a clinical indication for a single-chamber pacemaker (according to the evaluation of the centre). There were no exclusion criteria. The patients were recruited from four centres implanting the Micra TPS: the university hospitals of Geneva and Lausanne and the regional hospitals of Fribourg and Sion.

The Micra TPS is a self-contained single-chamber ventricular pacemaker. It has a volume of 0.8 cm^3, a length of 25.9 mm, and a weight of 2.0 g (*Figure 1*). It has similar functions as a traditional single-chamber pacemaker with features such as rate-adaptive pacing, automated capture thresholds, etc. but with more limited memory functions and algorithms.

The device is inserted through the femoral vein via a 27-Fr external diameter introducer and positioned in the right ventricle, where it is fixated by four flexible nitinol tines (see *Figure 2*).

The procedure was performed in the catheterization laboratory of the four centres by seven different cardiologists who had all undergone specific training by the manufacturer.

Follow-up and endpoints

Data from the patients' files were reviewed regarding the implantation procedure, device follow-ups, and adverse events. When required, additional information was directly provided by the operators.

Charts were reviewed for procedure duration, fluoroscopy time, electrical parameters (capture thresholds, pacing impedance, and battery voltage), and complications.

Major procedure-related complications were defined as those which prolonged hospital stay, required a new admission, resulted in significant disability, were life-threatening or resulted in death through 6 months after implantation.

In order to compare procedure duration and fluoroscopy times with standard single-chamber pacemakers, data from the Swiss national pacemaker registry[7] were analysed for 2016. Data for all leadless pacemakers implanted in Switzerland from June 2015 to May 2017 were also extracted. The website automatically provides the user with averages and ranges for data for the chosen time period.

Statistical analysis

Statistical analysis was performed using the IBM SPSS v24 program. Data distribution was verified using histogram analysis and the Kolmogorov–Smirnov and Shapiro–Wilk tests. Electrical parameters showed a skewed distribution, and changes over follow-up were analysed using the Kruskal–Wallis test. Data are displayed as mean ± SD or median ± 25th-75th percentiles as appropriate. A two-tailed *P*-value of <0.05 was considered statistically significant.

Results

Patients

We included 92 patients implanted from June 2015 to June 2017, with last data collection at the end of June 2017, with a mean follow-up of 12.4 ± 7.4 months.

The baseline characteristics of our patients are presented in *Table 1*. The youngest patient was 22 years old and suffered from congenital high-grade atrioventricular (AV) block. The Micra TPS was implanted instead of a dual-chamber system according to the patient's choice. Only two patients were younger than 60 years, and the oldest patient was aged 96 years.

The reason for Micra TPS implantation instead of a conventional transvenous pacemaker was not detailed in the patient files. However, one patient had failed implantation of a transvenous device because of a persistent left superior vena cava, and four patients had a septic state that contraindicated a traditional transvenous pacemaker.

Four patients had a prior transvenous pacemaker, which had to be removed in two of them because of infection. The third patient had breast radiotherapy which needed removal of the pacemaker. The last patient had a transvenous pacemaker which was approaching end of life and preferred not to have device replacement by a conventional system.

Procedural success

Of the 92 patients undergoing implantation, 90 (97.8%) were successfully implanted. The two unsuccessful cases are detailed below (one death and one cardiac tamponade).

The mean procedure duration was 41 ± 22 min (range 16–129 min). The average duration of fluoroscopy was 6.7 ± 4.8 min (range 1–26 min) with a mean dose area product of 2630 ± 4594 $cGycm^2$.

According to data from the Swiss national pacemaker registry for the same 2-year period (June 2015–May 2017), a total of 289 Micra TPS leadless pacemakers were implanted across Switzerland. Mean procedure duration was 47 min (range 16–130 min) with a mean fluoroscopy duration of 9.4 min (range 1–60 min). In comparison to Micra TPS, implantation of standard single-chamber transvenous

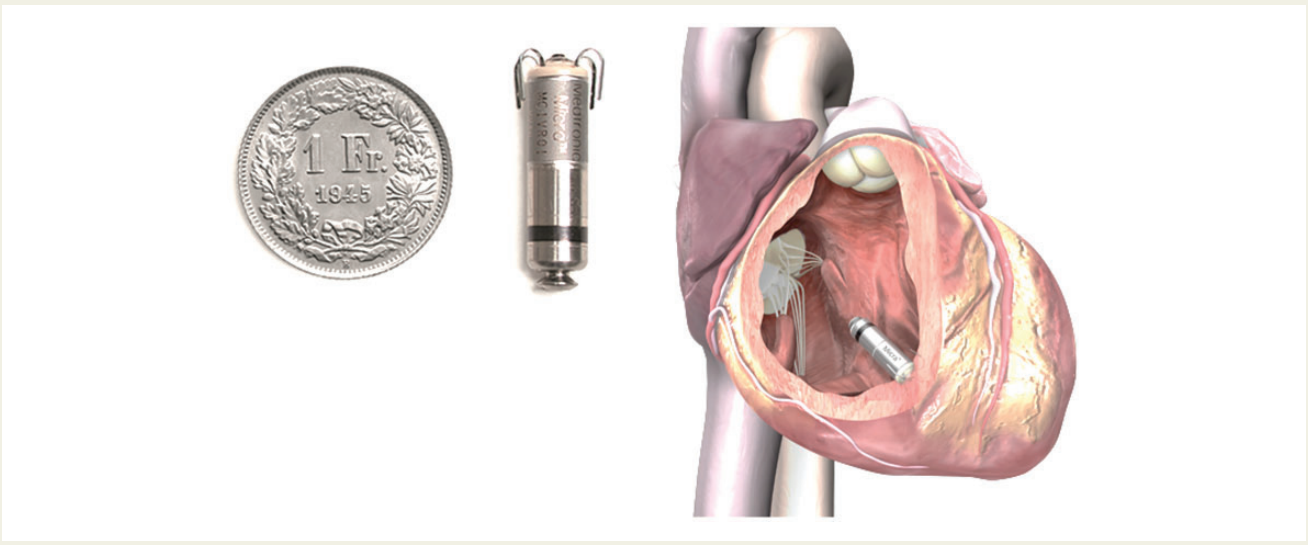

Figure 1 Micra TPS leadless pacemaker. Image adapted and reproduced with permission from Medtronic. TPS, transcatheter pacing system.

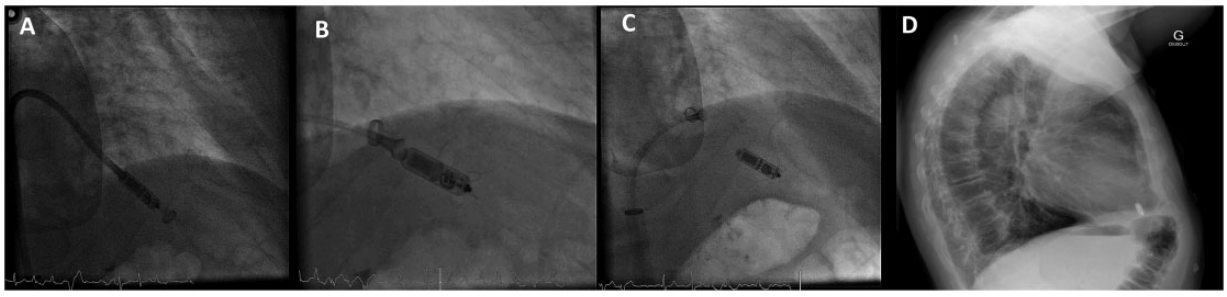

Figure 2 Implantation of a Micra TPS. (*A*) Positioning of the device in the right ventricular apex via a deflectable catheter. (*B*) Withdrawal of the sheath, exposing four nitinol tines which anchor the device to the myocardium; a tug test is performed by gently pulling on a suture which secures the device, and stretching of at least 2 of 4 tines is verified. (*C*) The device is freed by cutting the suture, and the sheath is withdrawn. (*D*) Lateral chest X-ray showing the device in the right ventricular apex (*A–C* are shown in the postero-anterior fluoroscopic views). TPS, transcatheter pacing system.

pacemakers ($n = 1320$) took on average 50 min with 5.3 min of fluoroscopy time (national registry data from 2016).

Electrical performance

The results are displayed in *Figure 3*.

Capture thresholds at implantation were low (median 0.38 V/0.24 ms, ranging from 0.13 to 2.88 V/0.24 ms). At Day 1 post-implantation, of the 90 implanted patients, 74 (82.2%) had a capture threshold <1 V/0.24 ms and four (4.4%) patients had an elevated threshold ≥2 V/0.24 ms, all of which were also elevated at implantation. Thresholds remained stable over follow-up.

Capture thresholds of ≥2 V/0.24 ms at 1, 6, and 12 months were observed in 6/78 (7.7%), 5/46 (10.9%), and 3/30 (10%) patients, respectively. One patient had an increase in capture threshold greater than 1.5 V from implantation to 6 months of follow-up. Except for this patient, all patients with elevated capture thresholds at baseline remained stable during follow-up.

Sensing amplitudes remained stable, but there was a significant reduction in pacing impedance over follow-up.

The mean battery voltage at 1 year (29 patients) was 3.04±0.04 V.

Procedure-related major complications

Perioperative complications

There were six major perioperative complications (6.5%) in six patients, from all four study sites, which led to prolonged hospitalization in five patients and death in one patient. The cases are detailed below:

(1) A death occurred in a 91-year-old diabetic and hypertensive female (with a body mass index of 25 kg/m^2) with heart failure and 2nd degree AV block. During attempts at positioning the Micra TPS across the tricuspid valve (and before positioning the device at the apex), the patient presented with tamponade and haemodynamic collapse. Despite emergency pericardiocentesis and reanimation, the patient could not be resuscitated. An autopsy was not performed, and it is

assumed that the device had perforated the atrial appendage. This was the operator's 7th patient, without subsequent major perioperative complications in the following 32 patients.

(2) A second case of cardiac tamponade and haemodynamic collapse occurred in a 76-year-old female with sick sinus disease and paroxysmal AF while delivering the device at the right ventricular apex. She was successfully reanimated with pericardiocentesis. The procedure was interrupted, and the patient refused any further implantation. This was the 8th implantation of the operator.

(3) A 79-year-old male patient with AF and symptomatic bradycardia experienced a local complication with haematoma and active bleeding at the groin puncture site (despite prior interruption of anticoagulants and a haemostatic figure-of-eight suture at the puncture site after sheath withdrawal). External compression was required, subsequently with extensive ilio-femoro-popliteal deep vein thrombosis. The patient ultimately required inferior vena cava filter placement. He was treated in the hospital for a total of 30 days and received transfusion of three units of packed red blood cells. The complication occurred in the 9th patient of an operator with 15 years' experience in large-bore femoral venous access for lead extractions.

(4) Another local complication occurred in an 86-year-old male patient with three-vessel coronary artery disease and paroxysmal AF. He was implanted with a Micra TPS because of second degree Mobitz II AV block. During the intervention, after three deployments the TPS catheter was removed for inspection due to high thresholds and a voluminous thrombus was found at the distal extremity. The operator changed the device, and a new TPS was successfully deployed with a low pacing threshold. A routine transthoracic echocardiogram showed a thrombus attached to the tricuspid valve (which was absent on the preoperative recording). He received intravenous therapeutic heparin and the thrombus disappeared. At 48 h post-implantation, he presented with haemodynamic instability (hypotension and tachycardia) with a haemoglobin drop requiring transfusion of two units of packed red blood cells. An 8 × 5 cm haematoma without active bleeding was found at the right groin puncture site. He was discharged after 5 days of conservative management. This was the 8th patient of the operator.

(5) A 70-year-old patient with slow atrial fibrillation (AF), 50% left ventricular ejection fraction (LVEF), two-vessel coronary artery disease, and hypertension, experienced during catheter handling two episodes of unstable ventricular tachycardia which required emergent electrical cardioversion. The device was finally positioned after three deployments without any further arrhythmia during the procedure and the following 24 h during which the patient's rhythm was monitored.

(6) A 75-year-old patient with symptomatic bradycardia and permanent AF, moderate aortic stenosis, coronary artery disease, and normal ejection fraction, suffered from intense tearing chest pain during the implantation, which persisted during the days following the procedure. A complete work-up was performed and a cardiac, pulmonary, or gastro-intestinal aetiology could be ruled out. The suspected cause was a musculoskeletal pain related to the position during the procedure.

Table 1 Baseline characteristics

Characteristics	Patients (n = 92)
Age (years)	80.3 ± 11.1
Male	60 (65%)
LVEF (%)	57 ± 10
Pacing indication	
Bradycardia with atrial arrhythmia	47 (51.1%)
Sinus rhythm with AV block	22 (23.9%)
2nd degree AV block	6 (6.5%)
3rd degree AV block	16 (17.4%)
Sinus node dysfunction	16 (17.4%)
Carotid sinus hypersensitivity	7 (7.6%)
Comorbidities	
COPD	16 (17.4)
LBBB	15 (16.3)
Peripheral vascular disease	16 (17.4)
Coronary artery disease	43 (46.7)
Valvular disease	30 (32.6)
Chronic renal failure	28 (30.4)
Prior pacemaker	4 (4.3)

Data shown as n (%) or mean ± SD.
AV, atrioventricular; COPD, chronic obstructive pulmonary disease; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction.

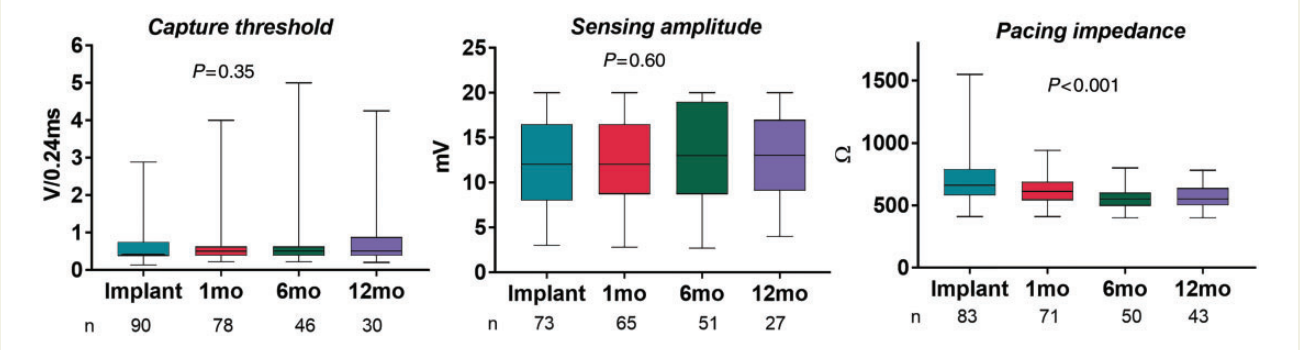

Figure 3 Electrical performance of the Micra TPS at implantation and over 1-year follow-up. Boxes correspond to median and 25th to 75th percentiles, and whiskers correspond to minimum and maximum values. mo, months; TPS, transcatheter pacing system.

Complications during follow-up

Three (3.3%) major complications occurred during a mean follow-up of 12.4 ± 7.4 months.

Two patients had elevated capture thresholds (4.25 V/0.24 ms and 4.0 V/0.24 ms) which required implantation of a traditional transvenous system at 2 and 13 months post-implantation, respectively. Of note, capture thresholds were already elevated at implantation for these two patients at 2.5 V/0.24 ms and 2.0 V/0.24 ms, despite multiple deployments of the system (3 and 5, respectively) with the devices being left in an apical position in the hope that thresholds would improve over time. The Micra TPS were left in place, and there were no complications with the transvenous implantations.

The patient who required electrical cardioversion for ventricular tachycardia during implantation was admitted 2 months later with recurrent haemodynamically unstable monomorphic ventricular tachycardia at 180–220 b.p.m. Despite amiodarone, beta blockers, verapamil, lidocaine, and external defibrillation, the ventricular tachycardia persisted. Radiofrequency catheter ablation was performed after having mapped the tachycardia to the interventricular septum via transseptal access, close to the insertion site of the Micra TPS. Application of up to 50 W of radiofrequency energy resulted in slowing and interruption of the arrhythmia. The ventricular tachycardia however recurred, with gradual acceleration (suggesting an automatic mechanism) after the end of the procedure. The patient underwent emergent surgical explantation of the Micra TPS, following which the arrhythmia resolved over the next 2 weeks (under amiodarone which had been previously introduced to treat AF). An MRI revealed asymmetrical septal hypertrophy with an LVEF of 50%, without ischaemia. A standard single-chamber pacemaker was implanted, and he was finally discharged after a 40-day hospitalization, with an uneventful course during the following 3 years of follow-up.

There were no cases of embolization of the device or infection.

Mortality at follow-up

There were 19 deaths (20.7%) during follow-up, none of which were presumed to be directly related to the Micra TPS. Among these deaths, 4 occurred due to terminal cardiac failure, 1 due to stroke, 2 to ischaemic colitis, and 12 of unknown causes.

Discussion

The main findings of our study were that: (i) implant success was high and comparable with previous reports; (ii) electrical parameters at implantation and over follow-up were good and comparable with previous data; (iii) the rate of major complications was 9.8% and higher than previously reported.

The implant success rate was high, with procedure durations comparable to those previously reported in the first publication on Micra TPS implantation (total procedure time 34.8 ± 24.1 min, fluoroscopy time 8.9 ± 16.6 min).[4] Implantation duration in our series was also comparable to that of standard single-chamber pacemakers in Switzerland (47 min vs. 50 min, respectively), with slightly longer fluoroscopy durations (9.4 min vs. 5.3 min, respectively). Patient X-ray exposure is likely to be significantly higher for Micra TPS implantation because high-quality cine acquisitions are necessary to verify proper anchoring of the tines (this is mitigated for the operator who is positioned at the patient's groin).

Capture thresholds were low, as previously reported,[4] which is important for device longevity. High thresholds (≥2 V/0.24 ms) were encountered in 10.9% of patients at 6 months, which is higher than the 2% for previously reported data.[4] Thresholds were stable over follow-up. As previously reported,[4] pacing impedances decreased over time, which may reduce battery longevity as this results in a higher current drain.

Our series had a high rate of major complications (6.5% perioperative and 3.3% over follow-up). This is much higher than previously reported (1.5% at 30 days[6] and 4.0% at 6 months[4]). This is the first publication of a per-operative death directly related to the procedure. Mortality may be under-reported in the literature for a variety of reasons (e.g. patients not being included in a registry). It should however be noted that Medtronic automatically reports all cases of perioperative deaths of which they are aware of to the MAUDE database, so it is likely that the majority of cases have been disclosed. Fatal intra-procedural outcome due to tamponade has been reported in 12 patients implanted with a Micra TPS in this database at the time of submission of this article.[8]

We speculate that tamponade resulting from Micra TPS implantation may be more serious than that caused by a standard pacing lead, due to the size of the device. This underscores the importance that emergent pericardiocentesis is available on site as a bailout for tamponade and that the paramedical staff is trained for reanimation. The French Society of Cardiology recently published recommendations suggesting that these devices should only be implanted in centres with cardiac surgery because of the exceptional need for emergency thoracotomy and risk of femoral vascular tears.[9]

Another complication was life-threatening ventricular arrhythmia, which occurred at implantation and at follow-up in one patient and resolved only after emergent surgical device explantation. A pro-arrhythmic effect of the fixation tines was most probably responsible for the event. It should be mentioned that the Micra TPS currently does not store electrograms of ventricular arrhythmias, and in case of syncope, this diagnosis should be considered. There is a recent publication of ventricular premature beats presumably induced by a Micra TPS (the extrasystoles had an identical morphology as the paced beats) which triggered polymorphic ventricular tachycardia, and required percutaneous extraction of the device.[10]

There may be several explanations for the higher complication rate observed in our report compared to the literature. Our patient population was considerably older (on average 80.3 years vs. 75.9 years in the investigational study[4] and 75.2 years in the post-approval registry[6]), and with more comorbidities especially coronary artery disease, pulmonary disease, and chronic renal failure. Importantly, this report includes the initial experience of all the operators, and complications (as well as the relatively high proportion of elevated capture thresholds) are likely to have been affected by their learning curve. The two cases of cardiac tamponade occurred in the very early experience of the operators and were not encountered thereafter. However, other complications may have been unrelated to the learning curve of this procedure (such as ventricular arrhythmia, or the venous access issue encountered by an operator experienced with large-bore femoral access).

In a recent EHRA survey,[11] 64% of operators perceived leadless pacemaker implantations as being 'easy and safe'. Nevertheless, our report stresses the importance of proper training (including

virtual-reality simulators), as the procedure is very different from that of conventional devices, with potentially serious complications. Furthermore, it is advisable that very close attention is paid during the initial experience of implanters (e.g. for the first 10 cases), ideally with the support of peers. As with any procedure, initial experience should be consolidated and maintained by a sufficient caseload thereafter. The French Society of Cardiology suggests a minimum of 20 implantations per medical centre per year with a maximum of two operators.[9]

It was surprising to note that patients in sinus rhythm with AV block, sinus dysfunction, or carotid sinus hypersensitivity were implanted with a single-chamber pacemaker, as a dual-chamber device is indicated according to current guidelines.[12] Reasons for choosing an intra-cardiac pacemaker over a standard device were rarely available in the patient files. Advanced age, cognitive disorders, and other comorbid conditions or low percentage of pacing may have influenced the choice of pacemaker type. As this study reports the initial experience with the Micra TPS, the novelty of the device probably might have influenced the investigators' choice as well. There are currently no international recommendations on the use of leadless pacemakers. Recently, the French 'Commission nationale d'évaluation des dispositifs médicaux et des technologies de santé' recommends intra-cardiac pacemakers mainly for adults at high risk of lead-related complications (history of lead fracture) and in whom veins must be spared (undergoing chemotherapy or haemodialysis) as well as patients without venous access and with a high risk of infection (history of endocarditis or septicaemia).[9] Patient life expectancy is an important factor, as additional devices will be implanted upon battery exhaustion (depleted device will be inactivated and not explanted). Omdahl *et al.*[13] demonstrated on six human cadaver hearts that up to three devices could be accommodated in the right ventricle without physical interaction. Exceptionally, young patients may be implanted with a Micra TPS in order to delay implantation of a transvenous system, as was the case in the youngest patient in our series, aged 22 years.

Limitations

Our study sample size is relatively small with only 92 patients. The retrospective nature of our study means that data may have been missed (e.g. minor complications, which were not reported in the patient files). The training received by some of the operators by the manufacturer at the launch of the device has since been modified and may not reflect that currently dispensed to new operators (thus possibly impacting complication rates).

Conclusions

Intra-cardiac leadless pacemakers represent a technological accomplishment and a paradigm shift in device therapy. Clearly, they are of benefit in selected patients, such as those with venous access issues or at risk of pocket/lead complications. More widespread use of these devices as a substitute for conventional transvenous pacemakers should however be carefully weighed against the longevity of the device (limited to ~10 years—at the term of which a new device needs to be implanted), the risk of complications (which, as shown by our report, are by no means negligible—at least during initial operator experience), as well as their cost (roughly 50% more than a conventional single-chamber pacemaker in Switzerland).

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References

1. Spickler JW, Rasor NS, Kezdi P, Misra SN, Robins KE, LeBoeuf C. Totally self-contained intracardiac pacemaker. *J Electrocardiol* 1970;**3**:325–31.
2. Kirkfeldt RE, Johansen JB, Nohr EA, Jørgensen OD, Nielsen JC. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. *Eur Heart J* 2014;**35**:1186–94.
3. Udo EO, Zuithoff NP, van Hemel NM, de Cock CC, Hendriks T, Doevendans PA *et al.* Incidence and predictors of short- and long-term complications in pacemaker therapy: the FOLLOWPACE study. *Heart Rhythm* 2012;**9**:728–35.
4. Reynolds D, Duray GZ, Omar R, Soejima K, Neuzil P, Zhang S *et al.* A Leadless intracardiac transcatheter pacing system. *N Engl J Med* 2016;**374**:533–41.
5. Duray GZ, Ritter P, El-Chami M, Narasimhan C, Omar R, Tolosana JM *et al.* Long-term performance of a transcatheter pacing system: 12-month results from the Micra Transcatheter Pacing Study. *Heart Rhythm* 2017;**14**:702–9.
6. Roberts PR, Clementy N, Al Samadi F, Garweg C, Martinez-Sande JL, Iacopino S *et al.* A leadless pacemaker in the real-world setting: the Micra Transcatheter Pacing System Post-Approval Registry. *Heart Rhythm* 2017;**14**:1375–9.
7. Groupe de travail stimulation cardiaque et électrophysiologie de la SSC. *Statistiques Annuelles* 2017. www.pacemaker.ch. (18 February 2018, date last accessed)
8. www.accessdata.fda.gov. (24 June 2018, date last accessed).
9. Defaye P, Klug D, Anselme F, Gras D, Hermida JS, Piot O *et al.* Recommendations for the implantation of leadless pacemakers from the French Working Group on Cardiac Pacing and Electrophysiology of the French Society of Cardiology. *Arch Cardiovasc Dis* 2018;**111**:53–8.
10. Amin AK, Billakanty SR, Chopra N, Fu EY, Nichols AJ, Kleman JM *et al.* Premature ventricular contraction induced polymorphic ventricular tachycardia after leadless pacemaker implantation: a unique adverse effect of leadless pacing. *Heart Rhythm Case Rep* 2018;**4**:180–3.
11. Boveda S, Lenarczyk R, Haugaa KH, Iliodromitis K, Finlay M, Lane D *et al.* Use of leadless pacemakers in Europe: results of the European Heart Rhythm Association survey. *Europace* 2018;**20**:555–9.
12. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA *et al.* ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Europace* 2013;**15**:1070–118. 2013;
13. Omdahl P, Eggen MD, Bonner MD, Iaizzo PA, Wika K. Right ventricular anatomy can accommodate multiple Micra transcatheter pacemakers. *Pacing Clin Electrophysiol* 2016;**39**:393–7.