Leadless Pacing with Micra TPS : a comparison between Right Ventricular Outflow tract, Mid-Septal and Apical implant Sites.

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Short Title: RVOT Pacing with the leadless pacemaker Micra TPS

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Word count: 2834 (including the abstract). Abstract only: 239 words

Contributors: All the authors contributed significantly to the completion of the study and the manuscript, including reading and approval of the manuscript in its current form.

Potential conflicts of Interest: RW/JE/CG research funding: Biotronik, Boston Scientific, Medtronic. Speakers and consultancy fees: Medtronic, Boston Scientific, Biotronik, St Jude Medical, Sorin. RW/JE are supported as postdoctoral clinical researcher by the Fund for Scientific Research Flanders.

Abstract

Background: With its steerable transcatheter delivery system, the Micra can be deployed in non-apical positions within the right ventricle, potentially allowing reduction of the paced QRS width. We sought to evaluate the safety and long-term performance of RVOT pacing using Micra TPS. We also compared the paced QRS between RVOT, mid-septal and apical implant positions.

Methods: All patients who underwent a Micra TPS implantation at the University Hospitals of Leuven were enrolled in this observational study. RV position of the device was assessed on per-procedural ventriculography. Paced QRS was analyzed and follow-up completed at 1 month and then each 6 months.

Results: Among the 133 patients included (mean follow-up: 13 ± 11 months), 45 were implanted in the RVOT, 58 midseptally and 30 at the apex. All implant procedures were successful and no pericardial effusion was encountered within the 30 days post-implant. Two major complications were reported with devices implanted at the apex. Pacing impedance was significantly higher in the RVOT compared to the mid-septal and apical position ($p < 0.001$). Pacing threshold and R-wave amplitude did not differ over time in either positions. The median narrowest paced QRS duration was observed in the RVOT (142 ms) compared to mid-septal (159 ms), ($p < 0.001$) and apical position (181 ms), ($p < 0.001$).

Conclusion: Implantation of the Micra TPS in the RVOT is safe and feasible. Electrical performance over time was comparable to mid-septal and apical positions. The narrowest paced QRS complexes is achieved with RVOT pacing.

Keyword: Micra TPS; leadless pacing, QRS duration; right ventriculography

Introduction

The Micra Transcatheter Pacing System (TPS, Medtronic, Minneapolis, MN, USA) is a leadless pacemaker that is implanted in the right ventricle to provide rate responsive ventricular pacing¹. During the initial experience, the device has been preferentially deployed in the right ventricular apex^{1,2}. Thereafter, the implantation of the device in a septal position has been associated with a reduction of major complications including cardiac perforation and effusion³. Recently, two reports have confirmed the safety and the favorable long term electrical performance of the mid-septal implantation of the device in high risk population^{4,5}. So far, the safety and the feasibility of pacing the right ventricular outflow tract (RVOT) with the Micra TPS and the relationship between the implantation sites and the paced QRS duration have not been investigated. Paced QRS duration is a known predictor of heart failure hospitalization in conventional pacing and has been shown to be longer when pacing the right ventricular apex compared with the RVOT⁶⁻⁸. In conventional pacing, non-apical pacing is associated with a reduction of QRS duration and seems to reduce the long term deleterious effects on cardiac function related to dyssynchronous activation of the heart during apical pacing⁹⁻¹¹. Therefore, the primary objective of this study was to report our experience of RVOT pacing with the Micra TPS in comparison with mid-septal and apical positions. The secondary objective was to compare paced QRS duration and pacing performance between apical, mid-septal and RVOT pacing positions using the Micra TPS.

METHODS

Patient population

We included consecutive patients who met class I or II guideline-based indication for pacing and who underwent implantation of a Micra TPS at the University Hospitals of Leuven between

July 2015 and December 2018¹². The protocol was approved by the Ethics Committee of the University Hospitals of Leuven.

Implantation procedure

All the Micra TPS were implanted according to the manufacturer's protocol described elsewhere^{1,2}. Briefly, the device equipped with four flexible nitinol tines need to be embedded in muscular trabeculations that are present from the apex to the lower portion of the RVOT. At the beginning of our experience with the Micra TPS, the targeted implant position was the RV apex before targeting the mid-septum and currently the RVOT.

Determination of Micra position with right ventriculography

To accurately determine the implantation position of the device, a right ventriculography was performed at the beginning of the implantation procedure in all patients. Therefore, a pigtail catheter was inserted via the femoral vein into the right ventricle and iodine contrast agent diluted to 50% (a total volume of 60 mL) was injected at a rate of 15 mL/s. Cardiac angiography was performed simultaneously from two directions (30° right anterior oblique [RAO] and 40° left anterior oblique [LAO] views with biplane cardiac digital angiography system (Siemens Axiom Artis dBC fluoroscopy system, Erlangen, Germany). Thereafter, Micra implantation was undertaken while integrating end-diastolic ventriculography images with biplane fluoroscopy. Micra position in the right ventricle was determined on RAO 30° view during diastolic phase and its septal deployment confirmed on 40° LAO view. There is a consensus view to say that the RVOT is anatomically defined as a trapezoid space between the tricuspid valve and the pulmonary valve, bounded anteriorly by the free wall of right ventricle and posteriorly by the upper part of interventricular septum^{13,14}. On RAO 30° view, the RV was divided into 3 areas as previously described by Kawakami et al¹⁵. The area above the supraventricular crest was defined as RVOT, the area under the supraventricular crest to the

level of the right ventricular anterior papillary muscle as the right ventricular inflow (mid septal position) and the area under the level of the right ventricular papillary muscle as the right ventricular apex (apical position) (figure 1).

Device electrical performance

Pacing threshold at 0.24 ms, R-wave amplitude and impedance were measured in all patients at implant, discharge, 1, 6, 12, 18 and 24 months.

Paced QRS duration and 12-lead Electrocardiogram

Resting 12-lead electrocardiograms (ECG) (25 mm/sec paper speed, 10 mm/mV) were collected before Micra TPS implantation and during VVI pacing at 90 beats per min to avoid fusion beats. QRS analysis was performed blinded from the Micra TPS position. QRS duration was automatically acquired by the Marquette 12SL™ ECG analysis program (GE Medical Systems, Menomonee Falls, WI) and was manually confirmed for all patients. Previously reported ECG characteristics for conventional RV pacing were also recorded: axis of the paced QRS, precordial lead transition, polarities in leads I, aVL and aVR, presence of a q-wave in lead I, presence of QRS notching in leads I, aVL and inferior leads and presence of isoelectric QRS in inferior leads^{16,17}.

Statistical analysis

Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. As all parameters showed a non-normal distribution, data are presented as median with the 25th and 75th percentile. Electrical parameters (pacing threshold, R wave sensing and pacing impedances) are presented as mean $\pm$ standard deviation. Categorical variables are presented as number and percentages. Continuous variables were compared between the three groups using non-parametric Kruskal-Wallis testing. Categorical variables were compared using the Chi² test. Follow-up was compared using repeated measures ANOVA with Bonferroni post-hoc

testing after testing for normal distributions. Sphericity was tested by the Greenhouse-Geisser test and both overall and within-groups evolution was compared according to the Micra TPS position. A p -value <0.05 was considered significant. All statistical analyses were performed using SPSS (IBM statistics, version 25).

RESULTS

Patient characteristics

One hundred thirty-three patients were included in the study with a total of 135 Micra TPS implanted. They were mostly male (61.7%), their ages ranged from 28 to 93 years old with a median age of 83 (76-86) years. They had a normal left ventricular function with median left ventricular ejection fraction of 55 (50-60) %. Renal function was also preserved with a median plasma creatinine of 1.10 (0.91-1.39) mg/dL (Table 1) without post-procedure deterioration. The most common primary indications for pacing were high degree atrioventricular block with underlying atrial fibrillation or sinus rhythm (47.4%) and atrial fibrillation with bradycardia (36.8%). In our population, atrial fibrillation was more frequent ($p<0.001$) in patients with a Micra implanted in the apical position (83.3%) as compared to the mid-septal (69.0%) and the RVOT (51.1%) positions. Patients with a device implanted in the RVOT position tended to be younger with less co-morbidities (arterial hypertension, ischemic cardiomyopathy and history of valve surgery) without reaching statistical significance ($p>0.005$).

Implant procedure results

Micra TPS implantation was successful in all patients at the initially targeted site. Two patients (the fourth and eightieth patients implanted by the operator) with an apically implanted device presented a significant pacing threshold increase during follow-up. The 4th patient had device repositioning in a mid-septal position during open heart surgery (combined mitral and tricuspid annuloplasty) while the 80th one was implanted with a new Micra TPS in the RVOT (without

retrieval of the first implanted device)¹⁸. No other major complications were observed at implant and during follow up. There was no cardiac effusion, no micro/macro-dislodgements nor perforation. Implant related minor complications were observed in six patients. Two patients experienced a severe vagal reaction at the beginning of the procedure promptly treated by atropine injection. Two patients presented a groin complication (one major hematoma requiring a prolonged hospitalization and one asymptomatic arteriovenous fistula at the puncture site with spontaneous healing at 4 weeks. Two patients developed a deep venous thrombosis within the two weeks following the implant procedure. Both evolved favorably under oral anticoagulation during 3 months.

Based on the right ventriculography, forty-five Micra TPS were implanted in the right ventricular outflow (figure 2), 58 in the mid septum (figure 3) and 30 in the right ventricular apex (Figure 4). The implant procedure duration (excluding time for the venous access) was 14.5 (10-28.5) min (range: 6-109 min) with a fluoroscopy time of 10 (8-16) min. Mean number of deployments was 1.7 ± 1.3 (range: 1-8). The first attempt of deployment was successful in 66.9% of procedures whereas 1 or ≥ 2 redeployments were respectively necessary in 21.1% and 12% of procedures. No significant differences in term of implant procedure characteristics were observed between the 3 positions except for the procedure duration ($p < 0.001$), the shortest duration being observed for the device deployment in the RVOT position.

Device electrical performance at the time of implantation and follow-up

Patients were followed up for an average of 13 ± 12 months (range 1 month to 36 months). On implantation, the pacing threshold was 0.52 ± 0.30 V/0.24 ms and the R-wave amplitude was 9.7 ± 4.6 mV. Those values were not statistically different between the three different Micra TPS positions and remained stable during follow up (figure 5A and B). On implantation, the pacing impedance was greater in the RVOT position (946 ± 292 Ohm) compared to the mid septal (792 ± 260 Ohm, $p < 0.05$) and apical (739 ± 240 Ohm, $p < 0.05$) positions. The difference

remained stable over time observing a constant decrease of the pacing impedance during follow-up for all positions ($p<0.001$) (figure 5C).

Twelve-lead electrocardiogram, paced QRS duration and Micra position

The characteristics of the paced QRS complex in relation with the Micra TPS implant location are presented in Table 2. The mean axis of the paced QRS was significantly associated with the position of the device ($p<0.001$). According to the right ventricular Micra TPS position, the paced QRS duration values were 142 (135-150) ms at the RVOT, 159 (150-165) ms at the right ventricular mid septum and 181 (174-189.5) ms at the right ventricular apex (Figures 1 to 3). The paced QRS duration was significantly longer in the apical as compared to the non-apical positions ($p<0.001$). The paced QRS duration was also significantly shorter in the RVOT position than at the mid-septum ($p<0.001$).

DISCUSSION

This is the first report to specifically consider the implantation of the Micra TPS in the RVOT and to provide direct comparison with mid-septal and apical positions of the device in a real-world population.

First, our results showed the feasibility and the safety of RVOT pacing using the Micra TPS. The acquisition of a biplane right ventriculography improves the recognition of the anatomical landmarks of the right ventricle providing more details than the usual fluoroscopy. The overlay of the right ventriculography on live fluoroscopy contributes to improve accuracy of device positioning. In our experience, it also improved the safety of the procedure by eliminating the risk of cardiac perforation related to inappropriate positioning of the device towards the right ventricular free wall. Importantly, the minimal use of contrast media (30 cc) was not associated with post-procedural renal function deterioration. There was a trend for less redeployments in non-apical positions and the shortest procedure duration was observed for the deployment of

the device in the RVOT. However, these results should be interpreted with caution because in our initial experience we implanted the Micra TPS in the apex. Therefore, this position compromises our learning curve. Later in our experience, our primary target moved from mid septal to the RVOT, which also favors the RVOT for the number of redeployments.

Secondly, our results showed that the RVOT position of the Micra TPS did not affect the acute and long-term electrical performance of the device as compared to mid-septal and apical positions. Loss of capture was only observed in two patients with an apically implanted device. Those adverse events occurred at the beginning and while the operator has gained experience with the implantation technique. Previously, Bongiorno et al. reported no difference of electrical performance between apical versus non-apical positions of the device⁴. It has to be noted that the authors did not separately consider the RVOT and the mid-septal positions of the device and only a minority of their patients were implanted in the outflow tract (8 RVOT versus 23 mid septal). In agreement with our results, safety was not affected by the deployment of the device in a non-apical position. However, these authors reported a higher number of deployments for devices implanted in a non-apical position without difference of procedure duration.

More recently, Hai et al also reported on the feasibility and the safety of septal leadless pacing in high risk population (advanced age, small body size and multiple comorbidities)⁵. Whereas the authors used fluoroscopic views of the cardiac silhouette to position the Micra, cardiac perforation occurred in one case because of inaccurate anchoring of the device in the right free wall. In the light of their results, the authors proposed the mid septal position as initial approach for implantation. Our results also demonstrated that alternative non-apical positions including the RVOT are safe and effective for Micra TPS implantation. This suggests that the operator could target either implant site in challenging procedures as in the presence of abandoned right ventricular pacing leads, the presence of a previously implanted Micra TPS (at the time of

device replacement) or in difficult RV anatomy. In theory, our results also validate the feasibility to implant a functional Micra TPS in three distinct RV positions. As such, they may forecast the feasibility of up to 3 successive Micra TPS implantations in the right ventricle over time as previously reported on human cadavers¹⁹. Finally, it is not excluded that the ease of device extracability/retrieval might be affected by its position in the right ventricle. It can be anticipated that it could be challenging to reach the RVOT using a steerable sheath like an AgilisTM NXT steerable introducer (Abbott Medical Inc. Abbott Park, IL, USA) to snare the Micra.

Pacing Site and Paced QRS duration

Pacing the right ventricle slows conduction through the myocardium resulting in QRS widening on the surface electrocardiogram¹¹. In patients with permanent pacing, the risk of cardiovascular death increases by 21% for each 10-ms widening in QRS duration²⁰. Several studies have also shown that the risk to develop heart failure, is associated with QRS duration. Therefore, a narrow paced QRS is preferable for long term prognosis^{6,8,20}. Paced QRS duration is determined by the site of pacing^{11,21}. The implantation of right ventricular leads in non-apical sites has been consistently associated with narrower paced QRS duration^{11,21}.

The paced QRS duration has not been studied in detail with the Micra TPS. Borgioni et al. have briefly commented on the shorter paced QRS duration when positioning the device in non-apical versus apical position but they did not compare either pacing sites (RVOT, septal and apical)⁴. Our study specifically evaluated for the first time the paced QRS duration with Micra TPS in 3 different positions. It showed that leadless pacing allows achieving a reduction of paced QRS duration as previously reported with conventional pacing. Non-apical pacing with the Micra TPS resulted in a significant reduction of the paced QRS duration compared to apical pacing. The shortest paced QRS duration was observed with RVOT pacing, suggesting that this pacing site should be preferred to decrease the risk of left ventricular function deterioration.

Study limitations

We report a non-randomized monocentric experience with only 133 patients which may limit the ability to detect differences between groups. The safety of the implant procedure in the non-apical position may have been increased by our sequential workflow as we first started to implant in an apical position. Moreover, since all the procedures were performed by the same operator under the guidance of a ventriculography, it is also conceivable that data on the safety of the implant procedure have been altered.

Conclusion

Micra TPS implantation in RVOT position is feasible and safe. Electrical performance during follow up is comparable between three ventricular positions. The narrowest paced QRS complex is achieved with RVOT pacing compared to mid-septal and apical pacing.

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Figure legends

Figure 1

Segmental anatomy of the RV as shown in right anterior oblique view. RV is divided in three different regions: RVOT, right ventricular inflow (mid-septal position) and RV apex.

Figure 2

Representative images of Micra delivery in RVOT position. Fluoroscopic views with overlaid ventriculogram on right anterior oblique (panels A and B) and left anterior oblique (panels C and D) incidences. Typical ECG tracing (panel E): negative QRS complex or qR morphology in I/aVL associated with positive QRS complex in inferior leads is usually observed in the RVOT position. On panels A and B, the ventricle is divided by the dashed lines into the three different locations: RVOT, mid-septum and RV apex.

Figure 3

Representative images of Micra delivery in mid septal position. Fluoroscopic views with overlaid ventriculogram on right anterior oblique (panels A and B) and left anterior oblique (panels C and D) incidences. Typical ECG tracing (panel E): positive QRS in I/aVL associated with QRS notching and isoelectric QRS in inferior leads suggests a mid-septal position. On panels A and B, the ventricle is divided by the dashed lines into the three different locations: RVOT, mid-septum and RV apex.

Figure 4

Representative images of Micra delivery in apical position. Fluoroscopic views with overlaid ventriculogram on right anterior oblique (panels A and B) and left anterior oblique (panels C and D) incidences. Typical ECG tracing (panel E): negative QRS complex in inferior leads associated with positive QRS in lead I/aVL strongly suggests an apical position. On panels A and B, the ventricle is divided by the dashed lines into the three different locations: RVOT, mid-septum and RV apex.

Figure 5

Electrical performance of Micra TPS Mean values and standard deviation. Pacing threshold (A) R-wave amplitude (B), pacing impedance (C). N values are the patients available at each time point.