

Clinical implications of novel technologies in pacemaker and cardiac resynchronization therapy

PhD thesis

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1. INTRODUCTION

In recent years, leadless technology in pacemaker (PM) therapy represents a fundamental paradigm shift. The new concept of a totally intracardiac PM can contribute significantly to the reduction of pocket- and lead-related complications. Nowadays, another rapidly emerging area of cardiac pacing is the development of new technologies for cardiac resynchronization therapy (CRT). Studies in this field are of particular importance when taking into account the prevalence of heart failure in Western countries.

Complications related to conventional cardiac device implantations are still notable. Leadless, intracardiac transcatheter pacing systems were developed to eliminate the most common complications associated with conventional PM therapy. In the two large, leadless PM trials, the typical complications of conventional PM implantations were disappeared, but femoral vascular complications and cardiac perforation with more serious consequences occurred. Cardiac perforation is also one of the most serious complication of conventional transvenous PM lead implantation. Although various data is available about lead perforation, a detailed comprehensive analysis of this complication is lacking.

Chronotropic incompetence is defined as the inability of the heart to increase its rate adequately during exercise. The insufficient increase in cardiac output could result in symptoms and reduced quality of life. Conventional PM systems are capable with their motion sensors to increase the pacing rate in response to physical activity for a long time. Adequate accelerometer-based rate adaptive pacing can be challenging in leadless PMs because the device is inside the continuously moving heart. Micra PM uses a novel three-axis accelerometer sensor to detect physical activity while simultaneously filtering out the cardiac motion.

Atrial fibrillation (AF) is a very common arrhythmia in patients with heart failure and reduced ejection fraction (HFrEF). Tachyarrhythmia can lead to left ventricular dysfunction and worsening heart failure can induce AF as well. Reduced efficacy of

CRT in some patients with AF has been primarily attributed to loss of atrioventricular (AV) synchrony and suboptimal biventricular pacing. Accurately determining the amount of effective biventricular pacing being delivered had technical difficulties till now. A new device-based diagnostic feature is available in some modern CRT defibrillator (CRT-D) devices, which can accurately quantify the amount of effective CRT (%eCRT). A novel algorithm (eCRTAF) using the %eCRT diagnostic has been developed to increase the amount of effective CRT delivered during AF.

2. AIMS

I. Detailed objectives of our studies relating to leadless PM were:

1. To provide a comprehensive literature review on the incidence of cardiac perforation with conventional and with leadless PM systems.
2. To analyze the potential risk factors and protective factors associated with cardiac perforation.
3. To test the novel 3-axis accelerometer during rest and exercise and to classify the different qualities of activity vectors.
4. To analyze the stability of activity vector quality during short- and midterm follow-up.
5. To assess the need for activity vector testing in patients programmed to VVIR mode.

II. The objective of the CRTee study was the following:

1. To determine in HFrEF patients who receive CRT, whether the novel eCRTAF algorithm increases the amount of effective CRT delivered during AF compared to a currently available rate regularization algorithm (CAFR).

3. METHODS

3.1. Incidence of cardiac perforation with conventional and with leadless pacemaker systems: A systematic review and meta-analysis

3.1.1. Literature search and study selection

This study is in accordance with the PRISMA Statement and was prospectively registered in the PROSPERO database of systematic reviews (Registration number: CRD42016044099). A systematic search in PubMed, Cochrane Library, and Google Scholar databases was performed from 1990 to 2015. Only full-sized papers in English language, published in peer-reviewed journals reporting detailed data on PM lead related cardiac injury were considered. Studies eligible for inclusion were identified by using the following search strategy: 1st run: “lead perforation,” 2nd run: “cardiac perforation” OR “myocardial perforation” OR “pericardial effusion” OR “pericardial fluid” AND “pacemaker.”

The eligibility criteria for this meta-analysis were as follows:

- 1) Inclusion of patients undergoing conventional PM system implantations for standard indications.
- 2) Detailed data on the rate of cardiac perforation reported, defined as signs of periprocedural pericarditis, asymptomatic pericardial effusion or pericardial tamponade related to the implantation of atrial or right ventricular PM leads.

Studies reporting only pooled data for lead associated complications were not considered. Study design, patient characteristics, frequency, and timing of lead perforation, utilized lead and system types, rates of pericardial tamponade, need for lead revision/surgery, and independent risk factors for perforation were extracted from the selected studies. According to the onset of signs and symptoms, perforations were categorized as acute (perioperative or <24 hours),

subacute (occurring >24 hours but within 1 month after implantation), or delayed/chronic when appearing at later time.

3.1.2. Statistical analysis

Statistical analyses were conducted utilizing Comprehensive Meta-Analysis 3.3 (Biostat, Inc., Englewood, NJ, USA) and Microsoft Excel 2016 MSO (Microsoft Corp., Redmond, WA, USA). Event rates were synthesized using descriptive statistics: minimum and maximum, mean, weighted mean and median incidences were calculated. Given the overall low endpoint rates, the Peto odds ratio (POR) with 95% confidence intervals (CIs) was calculated from events and sample sizes for a head-to-head comparison of different system and lead types or lead positions. Heterogeneity between individual trial estimates was assessed using the Q statistic and I^2 statistic.

3.2. Physical activity detection in patients with intracardiac leadless pacemaker

3.2.1. Patient population and study design

Implantation and follow-up data were prospectively collected from all consecutive patients undergoing Micra implantation as part of the Micra Transcatheter Pacing Study at the Medical Center, Hungarian Defense Forces, Budapest, between February 2014 and September 2016. Patients with standard indication for single-chamber ventricular pacing were implanted. After device implantation, patients underwent a 5-minute exercise test at pre-discharge, and at 1, 3, 6 months postimplant and every 6 months thereafter. The device can detect activity for one vector at a time, so three separate measurements were needed each time to test all three available vectors. At the end of the 5-minute exercise test, the Micra device graphically visualizes the measured activity counts. On the basis of these findings the quality of

an activity vector was defined to be adequate (excellent or acceptable) or poor according to the following criteria:

- *Excellent activity vector*: when activity counts during walking were at least 10 counts higher than the highest recorded values in resting postures.
- *Acceptable activity vector*: when activity counts during walking were 5 to 9 counts higher than the highest recorded values in resting postures.
- *Poor activity vector*: when activity counts during walking were less than 5 counts above the highest recorded values in resting postures.

Both excellent and acceptable vectors could provide adequate activity detection during rest and exercise and thus were considered to be programmed for rate adaptive pacing. A subgroup analysis was additionally performed in patients programmed to VVIR mode at discharge to assess the stability of vector quality.

3.2.2. *Statistical analysis*

Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC). $P < 0.05$ was considered statistically significant. The results of the vector testing were synthesized descriptively. Logistic regression model was used to compare the performance and stability of the three accelerometer vectors.

3.3. The CRTEE (Cardiac Resynchronization Therapy Efficacy Enhancements) trial

3.3.1. Patient population and study design

It was a prospective randomized crossover study (NCT02222818) enrolling CRT patients with a history of AF. The study compared a commercially available algorithm (CAFR) with a novel algorithm (Effectiv CRT during AF [eCRTAF]). The primary endpoint was percent effective CRT (%eCRT) during AF. Additional endpoints were mean heart rate (HR) during AF and percent biventricular pacing (%Vp) during AF, which also included beats without left ventricular capture (ineffective beats). Cardiovascular adverse events also were recorded. The inclusion criteria included the following:

- A Medtronic Viva or Brava CRT-D had been implanted for at least 30 days
- AF burden: At least 6 days with at least 4 hours of AF during a 4-week period occurring within 90 days
- Being able to complete the LV Capture Management test
- Less than or equal to 97% Vp during AF.

Exclusion criteria were: AV nodal ablation, complete heart block, myocardial infarction within 30 days.

Baseline data were collected at the phase 1 visit, and the eCRTAF algorithm and the ambulatory diagnostics of %eCRT pacing were downloaded to the CRT-D devices using a modified model 2090 Medtronic programmer. Patients were then randomized 1:1 to either control (CAFR algorithm) or eCRTAF first. The phase 2 visit was scheduled when the programmed algorithm had been active for at least 2 hours or 4 weeks had passed, whichever came first. At the phase 2 visit, patients were crossed over to the alternative algorithm, and the process was repeated. After this phase, the exit visit was scheduled, or if desired, the eCRTAF algorithm could have remained on for up to 4 months postrandomization.

3.3.2. *Statistical analysis*

All analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC). For continuous variables, mean±SD were reported. For categorical variables, frequency and percentage were reported. The %Vp, %eCRT pacing, and mean HR during AF were compared between eCRTAF and control (CAFR) using paired t tests. P <0.05 was considered significant. A multivariate regression analysis was performed to identify factors that might be associated with greater increases in %eCRT pacing.

4. RESULTS

4.1. **Incidence of cardiac perforation with conventional and with leadless pacemaker systems: A systematic review and meta-analysis**

4.1.1. *Study Characteristics*

A total of 28 studies fulfilled the predefined selection criteria. These studies comprised 60744 patients undergoing conventional 1- or 2-chamber PM implantation. The two main publications of recently developed new leadless pacing systems were analyzed in comparison. Of all identified studies, only one was a randomized controlled clinical trial, whereas the remainder were post-hoc analyses of randomized trials or observational retrospective or observational prospective studies. The vast majority were single-center observations, with the exception of 8 multicenter studies, and 2 were based on national or industrial registries. Individual studies used different definitions of lead perforation including signs of periprocedural pericarditis, asymptomatic pericardial effusion, or pericardial tamponade. The postoperative follow-up ranged from 7 days up to 6.9 years.

4.1.2. Lead Perforation with Conventional and with Leadless PM Systems

The incidence of lead perforation ranged from 0% to 6.37% in individual studies with a mean of 0.82%, weighted mean of 0.31%, and median of 0.40%, respectively (Figure 1). A sensitivity analysis including only high-quality studies revealed comparable results (mean 0.71%, median 0.37%).

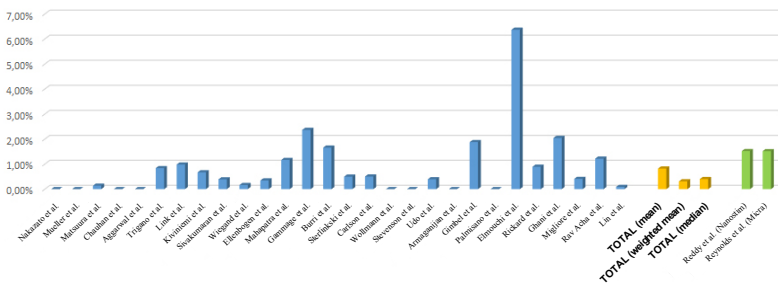


Figure 1. Incidence of pacemaker lead perforation in different studies.

The use of active fixation leads (POR 4.25, 95% CI, 1.00–17.95, $p = 0.05$, $I^2 = 69.8\%$), and utilization of DDD versus VVI systems (POR 3.50, 95% CI, 1.48–8.28, $p < 0.01$, $I^2 = 0\%$) were associated with higher rates of perforation.

Perforation rates reported in the 2 recent studies of leadless PMs appear to be remarkably similar, the incidence of cardiac perforation was 1.52% for each.

Descriptive details on other clinical characteristics potentially associated with lead perforation were available. Lateral or anterolateral atrial or apical right ventricular lead positions were

associated with elevated risk of lead perforation in some studies. Similarly, lead perforation was more frequent in female recipients and patients with more advanced age. Further predictors were use of previous temporary PM lead, treatment with oral steroids, or with aspirin/thienopyridines. In one report, elevated right ventricular systolic pressure (>35 mmHg) proved to be independently protective against lead perforation. These factors could not be subjected to meta-analysis due to the lack of studies reporting respective data in a controlled fashion. The timing of lead perforation varied among the 28 studies. Most perforations occurred within the first month after the implantation (subacute), and about one quarter of all perforations within 24 hours (acute). Delayed perforation (>1 month) was the rarest type of this complication.

4.2. Physical activity detection in patients with intracardiac leadless pacemaker

4.2.1. Patient characteristics

A total of 278 vector tests with 818 vector measurements in 51 patients with at least one repeated test were included in the current analysis. The median follow-up time for patients with repeated tests was 18 months (minimum: 3 months and maximum: 24 months).

4.2.2. Results of the initial vector tests

Vector 1 proved to be adequate (excellent in 22 patients and acceptable in 16 patients) in 74.5% of patients during the initial vector test. When looking across all three vectors, at least one excellent vector was found in 38 patients, and at least one acceptable vector was identified in an additional 10 patients leading to adequate test results in 94.1% of all patients. In three patients (5.9%) no excellent or acceptable vector was identified at the initial vector testing.

4.2.3. Evaluation of vector stability

Mid-term results of vector quality with repeated tests showed that Vector 1 remained excellent in 17 patients (33.3%) and was at least acceptable in an additional 16 patients (31.4%). At least one (initial or repeated) test of Vector 1 resulted in poor quality in 18 patients (35.3%). Vectors 1 and 3 showed similar mid-term results (adequate quality in 64.7% vs 68.6%; $p = 0.65$) and better results compared with Vector 2 (51.0%; $p = 0.10$ vs Vector 1, $p = 0.01$ vs Vector 3; Figure 2).

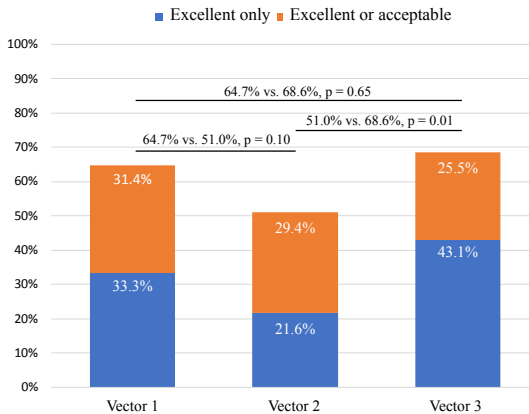


Figure 2. Results of the repeated tests for activity vectors.

4.2.4. Follow-up of patients programmed to VVIR mode

In our patient cohort, there were 45 patients with chronotropic incompetence programmed to VVIR mode after the initial vector test. Vector 1 was selected in only 46.7% of these patients. In the remainder of the patients (53.3%), a better alternative vector was

chosen (Vector 2 in 8.9% and Vector 3 in 44.4%). A vector change or modification of pacing mode was performed in 10 patients (22.2%) during follow-up. In four patients, the reason was signal quality drop; in an additional four patients, the initially selected vector was stable, but a vector with better quality was identified and selected. In three patients (non-apical right ventricular locations in all cases), the rate adaptive function had to be permanently deactivated because of poor vector quality during all repeated tests. There was not any change in the position of the Micra devices observed via chest X-ray in these patients.

4.3. The CRTee trial

4.3.1. Patient characteristics

Seventy-one subjects were enrolled in the study from 22 centers in the United States, Europe, and the Middle East between October 2014 and January 2016. Follow-up was completed in January 2016. Of the 66 subjects randomized, 54 had sufficient data (≥ 2 hours in each phase) available for analysis.

4.3.2. Primary results

During AF, the new eCRTAF algorithm resulted in a significantly higher %eCRT than control (%eCRT, $87.8 \pm 7.8\%$ vs $80.8 \pm 14.3\%$; $p < 0.001$), meeting both the primary objective of noninferiority and the secondary objective of superiority (Figure 3). The eCRTAF also resulted in a significantly higher %Vp during AF (%Vp, $90.0 \pm 5.9\%$ vs $83.2 \pm 11.9\%$; $p < 0.001$), and there was a small but statistically significant increase in mean heart rate of 2.5 bpm (79.5 ± 9.7 bpm vs 77.0 ± 9.9 bpm; $p < 0.001$) with the new algorithm.

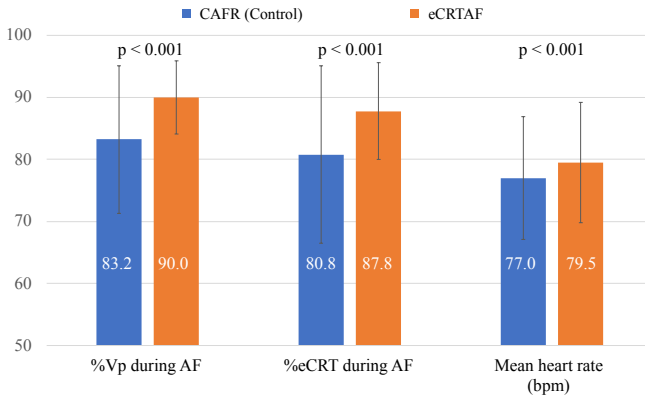


Figure 3. Effect of treatment on percent biventricular pacing (%Vp) (left), % effective CRT (%eCRT) (middle), and mean heart rate (right). Blue bars indicate control (Conducted AF Response [CAFR]). Orange bars indicate eCRTAF (EffectivCRT during AF). Error bars indicate standard deviation. AF: atrial fibrillation; CRT: cardiac resynchronization therapy

4.3.3. Subgroup analyses

Subjects with lower %Vp during the control (CAFR) phase showed a greater increase in %eCRT with eCRTAF than those who were already achieving a high %Vp. Subjects who received less than 80% Vp during control showed the greatest increase in both %Vp ($14.9 \pm 5.5\%$; $p < 0.001$) and %eCRT ($15.7 \pm 6.9\%$; $p < 0.001$) with eCRTAF compared to control. There was also an increase in mean HR of 2 bpm from 82 to 84 bpm ($p < 0.01$) in these subjects from control to eCRTAF. There was no significant difference in %eCRT or HR with eCRTAF in subjects with more than 95% Vp during control. A higher HR during control significantly reduced the increase in %eCRT with the algorithm ($p < 0.05$). Paroxysmal AF (as opposed to persistent or permanent AF) significantly increased the likelihood of a greater

increase in %eCRT with the algorithm ($p < 0.01$). None of the other factors considered had a significant effect.

5. CONCLUSIONS

1. Based on our meta-analysis of cardiac perforation we concluded the following:
 - 1.1. Conventional PM lead perforation rates varied in individual studies with an overall low incidence.
 - 1.2. The use of active fixation leads and utilization of DDD PM systems may be associated with higher rates of perforation.
 - 1.3. Perforation rates reported in the 2 recent studies of leadless PMs appear to be slightly higher compared to the conventional systems. This may reflect a learning curve effect of this novel technology or the difference in implantation techniques of these devices.
 - 1.4. A standard classification scheme of cardiac perforations would be advantageous for future research.
2. During the evaluation of the new Micra activity sensor we found the following:
 - 2.1. The novel 3-axis accelerometer-based rate adaptive pacing feature proved to be feasible after manual selection of an adequate activity vector.
 - 2.2. Activity vector selection based on vector testing appears to be more beneficial in 30-50% of Micra patients with chronotropic incompetence compared with the use of nominal Vector 1.
 - 2.3. The quality of activity vectors was stable after the 3-month follow-up, therefore repeated measurements are only required in selected cases.
3. The results of the CRTee study suggest:

- 3.1. In a cohort of CRT patients with a history of AF, eCRTAF significantly increased %eCRT pacing and %Vp during AF with a small increase in mean HR.
- 3.2. This algorithm may represent a novel noninvasive method of significantly increasing effective CRT delivery during AF, potentially improving CRT response.

6. OWN PUBLICATIONS

Publications related to the thesis:

1. **Bari Z**, Vamos M, Bogyi P, Reynolds D, Sheldon T, Fagan DH, Duray GZ. (2018) Physical activity detection in patients with intracardiac leadless pacemaker. J Cardiovasc Electrophysiol, 29: 1690-1696. [IF: 2,91 - 2018]
2. Vamos M, Erath JW, Benz AP, **Bari Z**, Duray GZ, Hohnloser SH. (2017) Incidence of Cardiac Perforation with Conventional and with Leadless Pacemaker Systems: A Systematic Review and Meta-Analysis. J Cardiovasc Electrophysiol, 28: 336-346. [IF: 2,873 - 2017]
3. Plummer CJ, Frank CM, **Bári Z**, Al Hebaishi YS, Klepfer RN, Stadler RW, Ghosh S, Liu S, Mittal S. (2018) A novel algorithm increases the delivery of effective cardiac resynchronization therapy during atrial fibrillation: The CRTee randomized crossover trial. Heart Rhythm, 15: 369-375. [IF: 5,225 - 2018]

4. **Bári Zs.** Vámos M, Bógyi P, Kiss RG, Duray GZ. (2017) Vezeték nélküli pacemaker: biztonságosság és működés a rendelkezésre álló klinikai adatok tükrében. *Cardiologia Hungarica*, 47: 219-224.

Publications irrespective of the thesis:

1. Bogyi P, Vámos M, **Bári Z**, Polgar B, Muk B, Nyolczas N, Kiss RG, Duray GZ. (2019) Association of Remote Monitoring With Survival in Heart Failure Patients Undergoing Cardiac Resynchronization Therapy: Retrospective Observational Study. *J Med Internet Res*, 21: e14142. [IF: 4,945 - 2019]
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7. Vámos M, **Bári Zs**, Polgár B, Kiss RG, Duray GZ. (2016) A pacemaker- és defibrillátor-beültetés során alkalmazott perioperatív antikoaguláns kezelés aktuális kérdései. *Cardiologia Hungarica*, 46: 17-22.
8. Lakner L, Csöngői V, Magyar L, Varga M, Miheller P, Sarlós P, Orosz P, **Bári Z**, Takács I, Járomi L, Sáfrány E, Sipeky C, Bene J, Tulassay Z, Döbrönte Z, Melegh B. (2009) Az 5q31 IBD5-régióban található IGR és SLC22A4/SLC22A5 variánsok lehetséges szerepe a gyulladással járó bélbetegség kialakulásában. *Orvosi Hetilap*, 150: 1375-1380.