Advances in cardiac pacemaker systems

Leadless and extracardiac pacing

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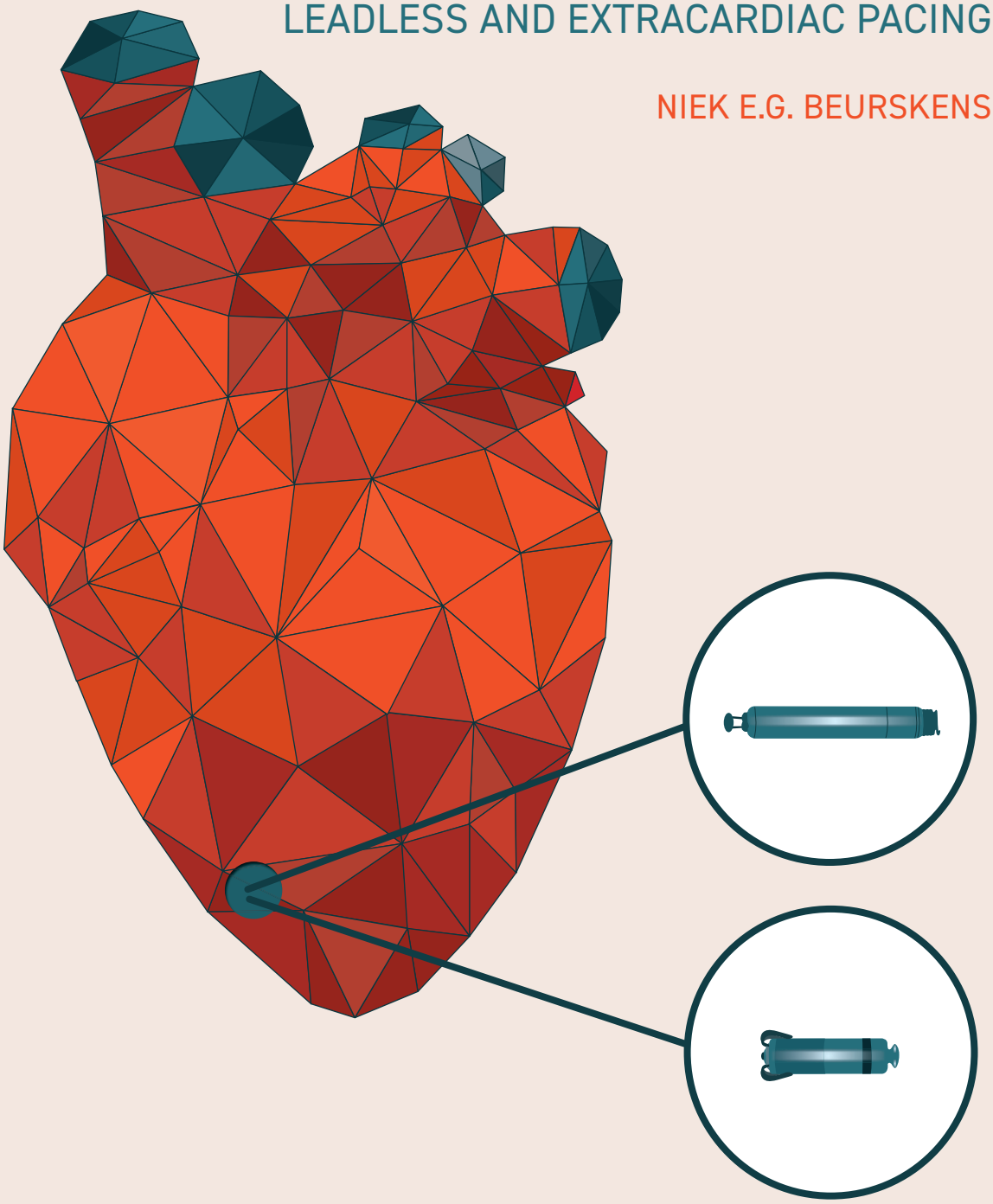
ADVANCES IN CARDIAC PACEMAKER SYSTEMS

LEADLESS AND EXTRACARDIAC PACING

NIEK E.G. BEURSKENS



Advances in Cardiac Pacemaker Systems

Leadless and Extracardiac Pacing

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Advances in Cardiac Pacemaker Systems

Leadless and Extracardiac Pacing

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CHAPTER

Introduction and thesis outline

Introduction

Epidemiology of pacemaker therapy

The worldwide annual pacemaker implantation rate is estimated to be around one million devices per year. (1-3) There are a number of observational studies available that provide an estimation of pacemaker implant rates per country in Europe, and they show that there is a huge difference between countries. (1-3) In some European countries less than twenty-five pacemaker implants are performed per million citizens whereas in other countries more than thousand pacing devices are inserted per million inhabitants. (1-3) In most cases cardiac pacing therapy is indicated in the elderly, with more than 80% of pacemakers being inserted in patients aged above sixty-five years.(3-10) The use of pacemakers continues to rise with the ongoing increase in life expectancy of populations worldwide and improving pacemaker technology. (3-10)

Development of pacemaker therapy

There is a high variety of indications for long-term pacing therapy. The most common remain: sinus node dysfunction and high-degree atrioventricular block. The natural course of both heart rhythm disorders is not entirely known because currently most patients undergo pacemaker implantation in an early stadium of the condition. There are some early observational studies available that report the survival of conservatively treated (i.e. non-paced) patients with high-degree atrioventricular block and sinus node dysfunction. (10-15) These studies show that mortality rates in untreated patients with high-degree atrioventricular block are approximately doubled in comparison to pacemaker recipients. In contrast, it is not evident that pacemaker therapy results in a longer life-expectancy in patients with sinus node dysfunction. (16,17) Yet, improving life-expectancy is not the only goal of pacemaker therapy, because the physical condition and quality of life are also key measures of treatment effectiveness. Studies have been unanimous in finding improved quality of life in patients receiving pacing therapy.(18-23)

Pioniers in the development of pacemaker therapy were doctor Rune Elmqvist and Ake Senning. In 1958, the physicians were the first that implanted an internal epicardial pacemaker system, yet the pacemaker failed within a short period of time. (24) In 1960, dr. Chardack, a thoracic surgeon, was the first to implant a battery powered pacemaker with a myocardial lead by using two surgical procedures (first the lead and subsequently a pulse generator). Major problems in pacemaker therapy remained common during the 1960s. It was not rare that pacemakers failed suddenly. Hence, multiple surgeries and replacements of parts or complete pacemaker systems were often required. Therefore, pacemaker therapy was not used as a routine treatment for a long period of time. Yet, this changed with the introduction of transvenous pacemaker therapy. Since then, with ongoing advances transvenous pacemaker therapy has become an essential treatment strategy

for various bradycardias in current clinical practice. In general, transvenous pacemaker implantation is considered a low-risk procedure. Nevertheless, complications related to the pacemaker pocket or pacemaker leads are not rare.(25) Therefore, there is always room for improvement in the dynamic field of pacing therapy. Among others, promising pacing alternatives that have been introduced in the last decade are for example his bundle pacing, left bundle branch pacing and leadless pacing.(26) His bundle and left bundle branch pacing provide a more physiological activation of the cardiac conduction system to decrease ventricular dyssynchrony associated with right ventricular pacing. The first clinical studies evaluating safety and effectiveness of his bundle and left bundle branch pacing are promising, yet additional studies are needed.(27-34) This thesis focusses on the alternative pacing approach to tranvenous lead-based pacemaker therapy: leadless pacemaker therapy. This novel pacing modality provides right ventricular pacing but does no longer require transvenous leads and a pacemaker pocket.

Leadless pacemaker therapy

In the 1970s, the first leadless pacemaker was developed and implanted in an animal study. (35) The concept of a pacemaker without wires or a pulse generator was very innovative and promising because it is generally known that the pacemaker leads and pocket are the main source of complications.(25) It took decades before the leadless pacing system was feasible for humans studies, because the battery longevity, reliability of the pacemaker, usability of the transcatheter delivery systems and communication techniques had to be developed and improved. Pioneer clinical studies were conducted only years ago. (36-38) There are two leadless pacemakers available in current clinical practice: the Nanostim leadless pacemaker and the Micra Transcatheter Pacing System. Both are intracardiac devices that are percutaneously implanted into the right ventricle through the femoral vein. Both have shown to be a reliable and effective treatment option for a selection of patients with bradyarrhythmias. (36-41) Although the new pacing approach is promising, there are some challenges that need to be further investigated, such as end-of-life management, learning curve, and the impact on cardiac and heart valve function.

Thesis outline

In this thesis, the current status of leadless pacemaker will be discussed including challenges of the pacing system. In addition, a new approach to pacing therapy will be introduced. **Chapter 2a** describes an illustrative case in which a transvenous pacemaker system could not be implanted in patient who required pacing therapy. In this case, implantation of a leadless pacemaker provided an adequate alternative. **Chapter 2b** provides a comprehensive overview of published data on the leadless pacemaker technology. In **Chapter 3**, it was investigated whether the leadless pacemaker might be an option for patients with a transvenous pacemaker infection. The impact of the Micra Transcatheter Pacing System on health-related quality of life was examined in **Chapter**

4. In part II of this thesis challenges of the leadless pacemaker are further investigated. In **Chapter 5**, the learning curve associated with the implantation of the Nanostim leadless pacemaker was evaluated. **Chapters 6a** and **6b** discusses the optimal end-of-life strategy of leadless pacemaker therapy and describes a case study in which it was applied. Furthermore, the impact of the intracardiac pacing device on cardiac and heart valve function was assessed in **Chapter 7.** In part III, **chapter 8** of the thesis, a novel pacing approach will be introduced: an entirely extracardiac, minimally invasive, temporary pacing system. Finally, **Chapter 9** and **10** provide an English and Dutch summary of this thesis.

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PART

I

Leadless Pacemaker Therapy

CHAPTER

2A

Percutaneous leadless pacemaker implantation in a patient with bilateral venous thoracic outlet syndrome

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We describe the case of a 71 year old patient with high grade atrioventricular block and sick sinus syndrome who was referred for implantation of a dual-chamber pacing system. Conventional pacemaker (PM) therapy requires a subcutaneous pacing generator and transvenous leads, commonly implanted via the subclavian vein. In patients in whom this transvenous route is not available, epicardial electrodes may be used as an alternative. The transvenous PM procedure failed because the right ventricle (RV) could not be reached by the subclavian venous route due to an obstruction. Contrast venography showed filling defects with extensive collateral veins formation confirming the stenosis in the left and right subclavian veins, suggesting the diagnosis of bilateral venous thoracic outlet syndrome (TOS). [Figure 1 A and B]

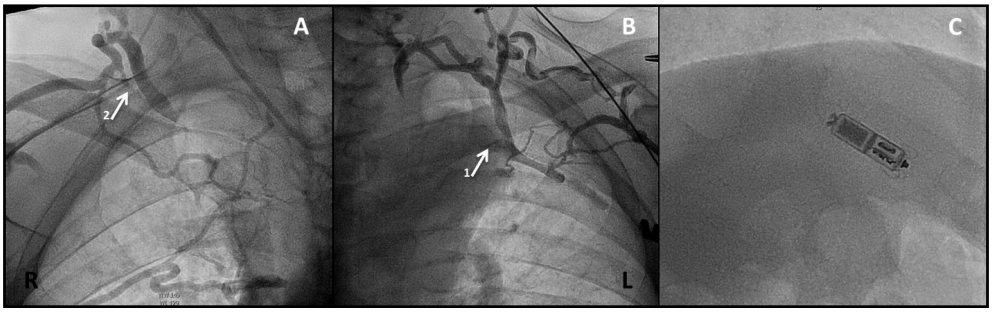

Figure 1. Contrast venography of the left *(Panel B)* and right *(Panel A)* subclavian veins. Arrow 1 represents the occlusion of the left subclavian vein. Contrast venography of the right subclavian vein showed a similar obstruction (Arrow 2). Extensive collateral vein formation can be seen around the occluded subclavian veins. *Panel C:* Chest X ray demonstrating the successful implantation of the Micra leadless pacemaker. The leadless pacemaker was intracardially implanted in the right ventricle via the percutaneous transfemoral route.

Therefore, the procedure was aborted. Thoracic outlet syndrome (TOS) is an uncommon vascular phenomenon, with an overall reported incidence of approximately 0.3% to 0.7%. [1,2] TOS can be categorized as vascular, including arterial or venous, neurogenic from brachial plexus compression, and a mixed form of neurogenic and vascular TOS.[1,2] Venous TOS accounts for only 3% of TOS cases.[3] Most of the deep vein thromboses in the upper extremity are secondary to catheters or indwelling devices. Review of a thoracic CT-scan performed several years previously to rule out pulmonary embolism showed the same vascular abnormalities, suggesting a long standing and stable condition. The patient had a very uncommon presentation of venous TOS since there were no clues in the patient's history as to the cause of the obstructions. No trauma, no excessive exercise, and no previous intravascular procedures were reported. Recently, a novel endovascular approach of pacing therapy has become available: a leadless pacemaker (LP) that is transfemorally inserted into the right ventricular cavity. Since our patient had a pacing indication, the use of a LP was considered as the most suitable alternative therapy. The LP (Micra: Medtronic Inc., Minneapolis, MN, USA) was inserted by a catheter delivery system through the right femoral vein with the use of a 23-French introducer.[4] The catheter

was inserted into the RV, and the LP was fixated to the myocardium in the apex with the nitinol tines located at the distal end of the device. The implantation was completed without complications and with adequate electrical parameters (right ventricular sensing of 9.7 mV, impedance of 740 ohm and a pacing threshold of 0.38 Volts at 0.24 ms). [Figure 1C] The patient was discharged one day post implant. The patient developed no complications during a follow-up of 1 year and resumed all normal activity. Our findings suggest that LP implantation is an effective solution in patients with a pacing indication affected by bilateral venous TOS. This situation might also apply to hemodialysis patients, who commonly need central venous catheters and where the presence of vein thrombosis or PM wires can be problematic. Although not addressed in current guidelines, this percutaneous approach may be considered as an alternative strategy for conventional transvenous dual chamber pacing in selected cases to avoid implanting an epicardial system.

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CHAPTER

2B

Leadless cardiac pacing systems: current status and future prospects

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Expert Rev Med Devices. 2019 Nov;16(11):923-930

Introduction: Permanent transvenous pacemaker therapy is an essential management option in patients with symptomatic bradyarrhythmias, but harbors a concomitant risk of serious complications. As most complications are lead- or pocket-related, intracardiac leadless pacemaker therapy has the potential to positively impact patient outcome. Since the first leadless pacemaker implant in 2012, many studies have been conducted to evaluate effectiveness, safety and applicability of this novel pacing approach.

Areas covered: This review will cover the current status of leadless pacemaker technology. Available safety and efficacy outcomes, current area of indication, and end-of-life management will be evaluated. Furthermore, future perspectives for clinical practice and new pacing modalities are discussed.

Expert opinion: The first-generation leadless pacemakers are a promising innovation that provide safe and efficient single-chamber pacing therapy without the use of transvenous pacemaker leads. Yet, broad implementation of this technology is hampered by limitations of the current leadless devices, such as end-of-life management and its single-chamber pacing indication. Further innovations such as leadless dual-chamber pacing therapy, leadless cardiac synchronization therapy, energy-harvesting leadless pacemakers, communicating leadless pacemakers with subcutaneous implantable cardiac defibrillators, and minimally-invasive completely extracardiac pacemakers are currently being developed that have the potential to become major game changers in pacing therapy.

Abstract

Introduction

Permanent pacemaker therapy remains a necessary treatment in patients with symptomatic bradyarrhythmias. The number of patients globally undergoing pacemaker implantation has increased steadily up to a current annual implant rate of ~1 million devices. (1, 2) The implantation rate continues to expand due to an aging population. (3) Pacing therapy results in health-related quality of life improvements and ameliorates prognosis in second degree type II or third degree atrioventricular (AV) block.(4, 5) Conventional transvenous pacemaker therapy is associated with a concomitant significant risk of complications, which are primarily lead- or pocket-related. Large nationwide multicenter cohort studies conducted in Denmark and the Netherlands demonstrated short-term transvenous pacemaker-related complication rates in 9.5 to 12.6% of patients. Lead-related interventions are the most frequently reported complications followed by pocket hematoma and pneumothorax. Long-term complications occur in an additional 9.2% of patients and consist mainly of lead dislodgment, stimulation threshold problems or discomfort of the pacemaker or pocket. Infection of a permanent implanted pacemaker is uncommon but is considered a serious complication and is associated with substantial morbidity and mortality. Current guidelines recommend complete hardware removal to mitigate the risk for severe systemic infection and infective endocarditis.(6-8)

In the 1970s, the idea of a pacemaker without leads or the need for a pectoral pulse generator was coined, hence bypassing the main source of complications of transvenous pacemaker system(9). Due to technological advances in battery longevity, communication techniques and transcatheter delivery systems, the leadless pacemaker became feasible for clinical implementation. Landmark studies in men were successfully performed only years ago(10-12). In this review, the current status of the technology will be discussed and summarized, including available clinical outcomes, indication area, end-of-life management and future perspectives. In addition, new pacing concepts and approaches will be discussed.

Leadless pacemaker therapy

To date, two leadless pacemaker variants have been developed for patients with a single-chamber (VVI) pacemaker implantation: the Nanostim Leadless Cardiac Pacemaker (LCP; Abbott) and the Micra Transcatheter Pacing System (TPS; Medtronic). The Nanostim LCP has been CE approved in 2013 and awaits Food and Drug Administration (FDA) approval after major callbacks due to early battery depletion and docking button detaching. The Micra TPS was CE approved in 2015 and subsequently FDA approved in 2016. **[Figure 1]** Both leadless pacemakers are fixated and fully contained in the right ventricle and provide similar functionality: right ventricular sensing / pacing and rate responsiveness.

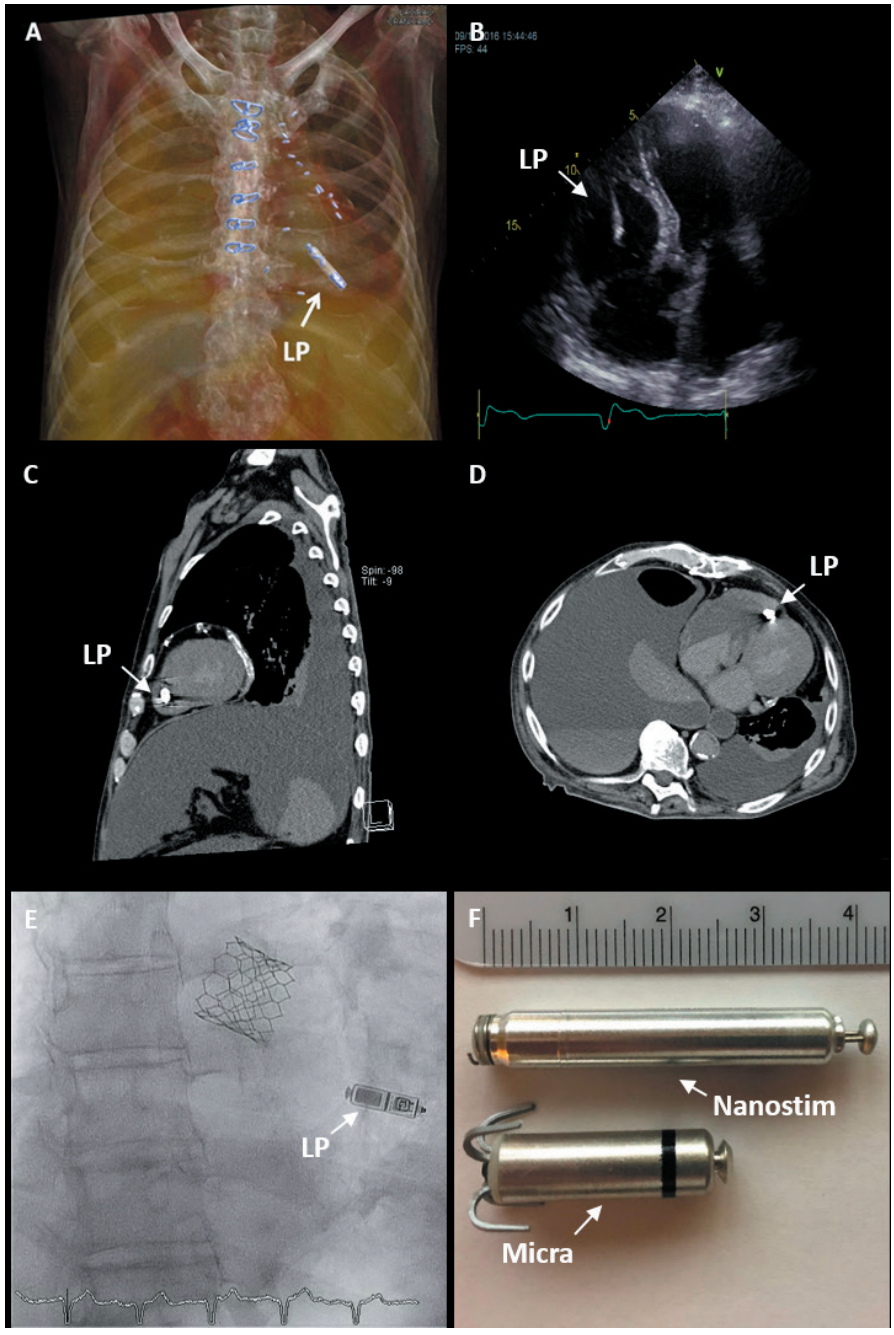

Figure 1. The Micra and Nanostim Leadless Pacemakers Leadless pacemaker therapy. Panel A: postmortem computed tomography (CT) with three-dimensional reconstruction of the Nanostim in the right ventricle. Panel B: transthoracic echocardiogram in apical 4-chamber view of the Nanostim in the right ventricle. Panel C: sagittal plane of a CT-scan of an in situ leadless pacemaker. Panel D: transverse plane of a CT-scan of an in situ leadless pacemaker. Panel E: radiogram of a Micra TPS after transcatheter aortic valve replacement. Panel F: photograph of the Nanostim LCP and Micra TPS.

The systems differ in size (LCP 42 mm; TPS 25.9mm), although having a comparable volume and weight (LCP 1.0 cc, 2 grams; TPS 0.8 cc; 2 grams). There are some differences between the Nanostim LCP and Micra TPS that should be emphasized. 1) The Nanostim LCP uses a thermal sensor and the Micra TPS a three-axis accelerometer as method of rate responsiveness. 2) For interrogation technology, Nanostim LCP uses ECG electrodes for limiting battery drainage, whereas the Micra TPS uses conventional radiofrequency currents. 3) The Nanostim LCP has a lithium carbon-monofluoride battery and the Micra TPS uses a silver vanadium lithium carbon-monofluoride battery. 4) The devices are anchored into the right ventricular myocardium in a different fashion: the Nanostim uses a screw-in-helix, whereas the Micra has 4 nitinol tines.

The systems are implanted in a similar fashion at the catheterization laboratory with fluoroscopic guidance. Dedicated introducer sheaths are used, which measure 18/21 French (inner/outer diameter) for the Nanostim LCP and 23/27 French for the Micra TPS. The leadless device which is mounted on a deflectable tip at the end of the delivery catheter, is introduced percutaneously through the femoral vein. Subsequently, the deflectable delivery system is advanced through the vena cava inferior towards the right atrium, across the tricuspid valve and anchored into the right ventricular myocardium. The device is fixated by either a screw-in helix (Nanostim LCP) or nitinol tines (Micra TPS). The optimal location of device placement in the right ventricle is determined by injecting radiographic contrast. After electrical threshold testing and determining stability with a tug test, the device is released from the delivery system.

Safety and efficacy of current leadless pacemaker systems

The first study to assess feasibility of the Nanostim LCP in humans was the LEADLESS trial. This was a prospective, single-arm, multicenter trial conducted in Europe and enrolled 33 patients. The primary safety endpoint was defined as freedom from serious device or implant-related complications at 90 days after implantation. There were 97% successful implantations (32 out of 33) and the primary safety endpoint was met with a complication-free rate of 94% (31 out of 33) (13). Two patients experienced serious complications: 1) perforation of the right ventricular apex resulting in cardiac tamponade and 2) incorrect placement of the leadless pacemaker in the *left* ventricular apex through a patent foramen ovale. Follow-up of this cohort until 12 months demonstrated no device-related complications and adequate performance results (i.e. pacing threshold, sensing amplitude, and impedance) (14). Subsequently, the clinical safety and effectiveness of the Nanostim LCP was tested in a prospective, nonrandomized trial with 527 patients, the LEADLESS II trial. The safety and efficacy endpoints were evaluated in the first 300 patients who reached 6 months of follow-up. The safety endpoint was met with freedom of complications in 93% (280 out of 300) of patients and the efficacy endpoint (i.e. pacing threshold, sensing amplitude, and

impedance) was met in 90% (270 out of 300) of patients. The LEADLESS Observational Study was a prospective, multicenter, nonrandomized trial, which reported safety of the Nanostim LCP in a real-world setting(15). The study was paused after 131 implantations due to some instances of cardiac perforation. After protocol changes and operator training, freedom from serious adverse events was observed in 95% (285 out of 300 patients) 6 months after Nanostim LCP implant. The most frequently reported complications were implantation-related, namely cardiac perforation (1.3%, n=4) and vascular complications (1.3%, n=4). Currently, a global stop for Nanostim LCP implantations is in place after the manufacturer issued a Medical Device Advisory in 2016 due to premature battery depletion. In these cases, abrupt battery failure leads to loss of pacing and communication functionality, which can be life-threatening in pacemaker dependent patients. Hence, immediate replacement of the non-functioning device – by a conventional transvenous pacemaker or a Micra TPS - is required in pacing-dependent patients.

Following preclinical testing of the Micra TPS, the first-in-human study to assess its safety and efficacy was the Micra Investigational Device Exemption (IDE) study(11). Similarly to the LEADLESS trial, the primary safety and efficacy endpoints were defined as freedom from serious adverse device events and stable electrical values, respectively. In this prospective, single-arm, multicenter study, both safety and efficacy end points were met. Freedom from serious adverse events was 96% and low and stable pacing thresholds were reported in 98.3% of patients 6 months post-implant. Serious adverse events included cardiac tamponade/effusion in 1.6%, events at the groin puncture site in 0.7% and elevated pacing thresholds in 0.3%. Real-world results of the Micra TPS were reported by the Micra Post-Approval Registry (PAR) including 795 patients(16). The 30-days major complication-free rate was 98.5%. As expected, the incidence of device-related complications in the Micra PAR study was lower than in the investigational Micra IDE trial. Later, the 12-month complication-free rate in 465 patients from the post-approval registry was 97.3% (17). The most frequently reported complications were pacing issues (0.7%), vascular complications (0.6%) and cardiac effusion/perforation (0.4%). The complication rate in the post-approval registry was lower than in the IDE cohort. Moreover, a >50% reduction in pericardial effusion rates was observed. Efficacy of the Micra TPS at 12 months was also confirmed with low and stable pacing thresholds. There have been no reported cases of early battery failure in the Micra TPS. In all abovementioned Micra TPS studies, the implant success rate was above 99%.

Quality of life must be regarded as a clinical endpoint of importance, especially in pacemaker therapy where improving prognosis is frequently not the core purpose of the treatment. In this respect, Micra TPS implantations were shown to improve health-related quality of life at 3 months and 12 months of follow-up(18). There is no data on Nanostim LCP and quality of life.

To date, there are no randomized studies to compare the safety and efficacy of leadless pacemaker therapy to the conventional method of transvenous pacemaker therapy. The most relevant comparative data on this topic comes from a propensity score-matched analysis comparing patient data from three experienced leadless implant centers with patients from a multicenter, prospective transvenous pacemaker registry(19). In the leadless pacemaker arm, 155 patients had a Nanostim LCP (i.e. 70%) and 55 out of 220 a Micra TPS implant (i.e. 30%); in the transvenous pacemaker arm, all 220 patients were implanted with a conventional VVI pacemaker. At 800 days of follow-up, the complication rate in the leadless pacemaker arm was 10.9% compared to 4.7% in the transvenous pacemaker arm. However, when excluding premature battery failures of the Nanostim LCP, the complication rate dropped to 0.9% in the leadless pacemaker arm. For the comparison of complication rates between both therapies, the latter-mentioned rate of the leadless pacemaker arm is thought to be most informative as implantations of the Nanostim LCP will only restart when the battery problem is resolved.

When interpreting data regarding safety of novel device therapies, the operator learning curve is an important aspect to keep into consideration. Implant success and safety from the highest quartile of operator experience (>10 implants) were compared with the lowest three quartiles in a large Nanostim LCP cohort (n = 1439). The complication rate was 4.5% in the highest quartile of operator experience, compared to 7.4% in the other quartiles - underscoring the existence of a learning curve. In contrast, major complication rate or pericardial effusion rate was not associated with case number in 726 Micra TPS implantations (20). Yet, the real world use of the Micra TPS showed a reduction in perforation from 1.6 to 0.4%.

Safety of leadless pacemakers in patients undergoing magnetic resonance imaging (MRI) studies is another important issue. Both Nanostim LCP (1,5T) and Micra TPS (1,5T and 3T) have been approved for MRI under specific conditions. In a small, prospective, observational study, 14 patients underwent MRI scans (1,5T, n = 7; 3T, n = 7) minimally 6 weeks after implantation of a Micra TPS(21). During three months of follow-up, no adverse events were noted and device parameters did not change significantly. Changes in device parameters did not differ significantly between 1,5T and 3T. Acquired MRI images are reported to be of good to excellent quality, providing good overall interpretation of MRI studies in patients with a leadless pacemaker(22). Due to the position of the leadless pacemaker infero-, antero- and apicoseptal images have most artefacts and may therefore be of impaired interpretability. No data regarding Nanostim LCP and MRI have been published yet.

Indications for leadless pacemaker therapy

Thus far, the only available pacing mode in leadless pacemaker therapy is VVI right ventricular pacing. This initially confined the area of indication of leadless pacemaker therapy to AV block with concurrent atrial fibrillation (including atrial fibrillation with slow ventricular response) (4). In patients with other indications for pacemaker therapy, atrioventricular synchrony can be maintained by implantation of leads in both the atrium and the ventricle, avoiding the risk of pacemaker syndrome(23). However, as every additionally implanted pacemaker lead carries an incremental risk of complications, the indication area for VVI pacing has broadened significantly(5). VVI pacing may currently also be indicated in patients with AV block or sinus node disease in which no frequent ventricular pacing is expected or in whom comorbidities are thought to determine clinical outcome. The minimal-invasive leadless pacemaker approach has specific advantages for elderly and frail patients such as less mobility restrictions and no risk of pocket erosions, and may therefore be preferred over single- or dual-chamber transvenous pacemaker therapy.

Transvenous pacemaker therapy requires extravascular and intravascular components that are susceptible to device infections. Reported infection rates of leadless pacemaker therapy are very low since the main sources of device infection – the pacemaker leads and pectoral pulse generator pocket – are eliminated. Therefore, specific patient populations with a high risk of device infection may benefit from leadless pacemaker therapy. In three studies, no recurrent device infections occurred in patients in whom a leadless pacemaker was implanted simultaneously or followed within months after extraction of an infected transvenous pacemaker (24-26). Furthermore, in patients on hemodialysis during implantation of a leadless pacemaker, no device infections were reported during follow-up(27). Finally, several case reports mention implantations of leadless pacemakers in patients with obstruction of the venous route used for transvenous pacemakers, such as bilateral venous thoracic outlet syndrome and chronic obstruction of the superior vena cava(28, 29).

End-of-life management

Albeit the positive results regarding safety and efficacy, one of the remaining challenges for leadless pacemakers is the strategy when reaching end-of-life. Effectively, the leadless pacemaker can either be extracted or abandoned before implanting a new device, which is common clinical practice in lead dysfunction in transvenous pacemaker therapy(30). For the Nanostim LCP, a dedicated catheter and single-loop or triple-loop snare retrieval system exists by which retrieval is considered safe and efficacious(31). For retrieval of

the Micra TPS no dedicated system exists, but successful retrievals are reported using a percutaneous gooseneck snare(32).

Preclinical animal experience demonstrated a 100% successful retrieval rate of the Nanostim LCP in eighteen sheeps up to approximately 2.5 years after implantation(33). A mid-term (n = 10; mean time from implant 160 days) and long-term (n = 8; mean time from implant 2.3 years) group were studied. Operation duration was 2.35 minutes in the mid-term group and 3.04 minutes in the long-term group, underscoring the ease of retrieval. Of note, the endocardial response to the Nanostim LCP was limited and there were no signs of significant adhesions of the leadless pacemaker and the right ventricular wall. The Micra TPS was retrieved in 3 out of 4 (75%) attempts in ovines up to 28 months after implantation(34). The unsuccessful retrieval was caused by complete encapsulation of the device.

Data on safety and feasibility of leadless pacemaker extraction in humans are limited. Most experience has been gained by retrievals of the Nanostim LCP due to the Medical Device Advisory. Replacement of the Nanostim LCP replacement for a Micra TPS is illustrated in **Figure 2.** (35)

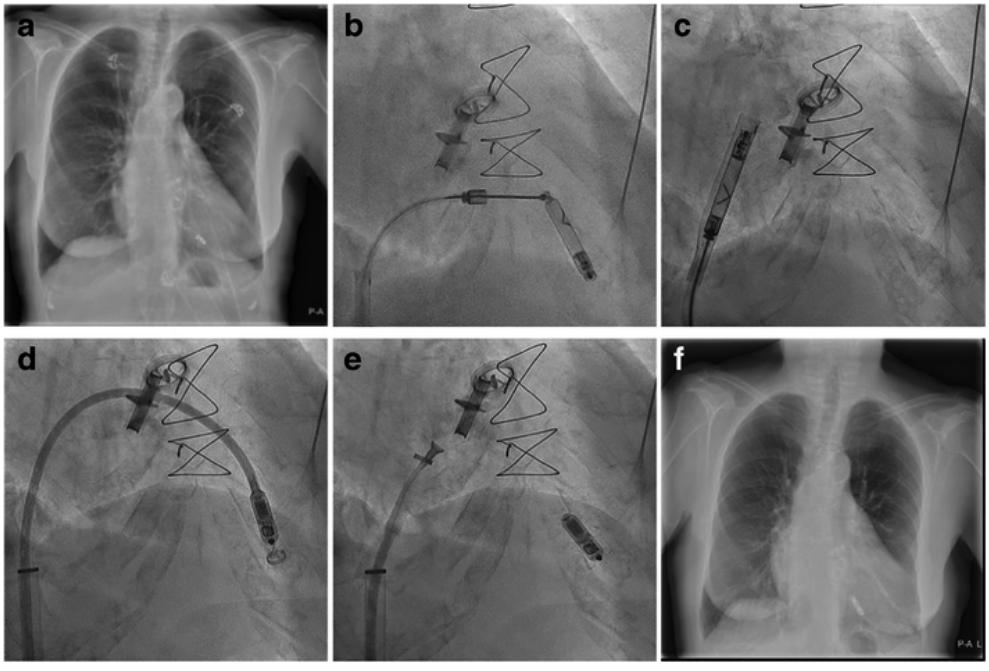

Figure 2. Replacement of the Nanostim for a Micra leadless pacemaker. Panel A: X-ray of a nonfunctioning in situ Nanostim leadless pacemaker. Panel B: the single-loop snare is looped around the docking button of the Nanostim. Panel C: Device extracted from the right ventricular cavity. Panel D&E: Micra TPS placement at a slightly different location in the right ventricle. Panel F: X-ray of the Micra TPS

Figure 3 illustrates an extracted Nanostim LCP mounted on the dedicated single-loop retrieval system. In the largest study thus far, retrieval data is reported on 73 attempts 0.2 - 4.0 years after implantation(31). Retrieval was successful in 66 (90.4%); in six patients the docking button was inaccessible and in one patient the docking button detached from the leadless pacemaker during retrieval and proceeded in the pulmonary artery. The latter was noted as a serious adverse event. One other leadless pacemaker retrieval-related serious adverse event was reported - the formation of an arteriovenous fistula. Time from implantation had no impact on successful retrieval rates in this study.

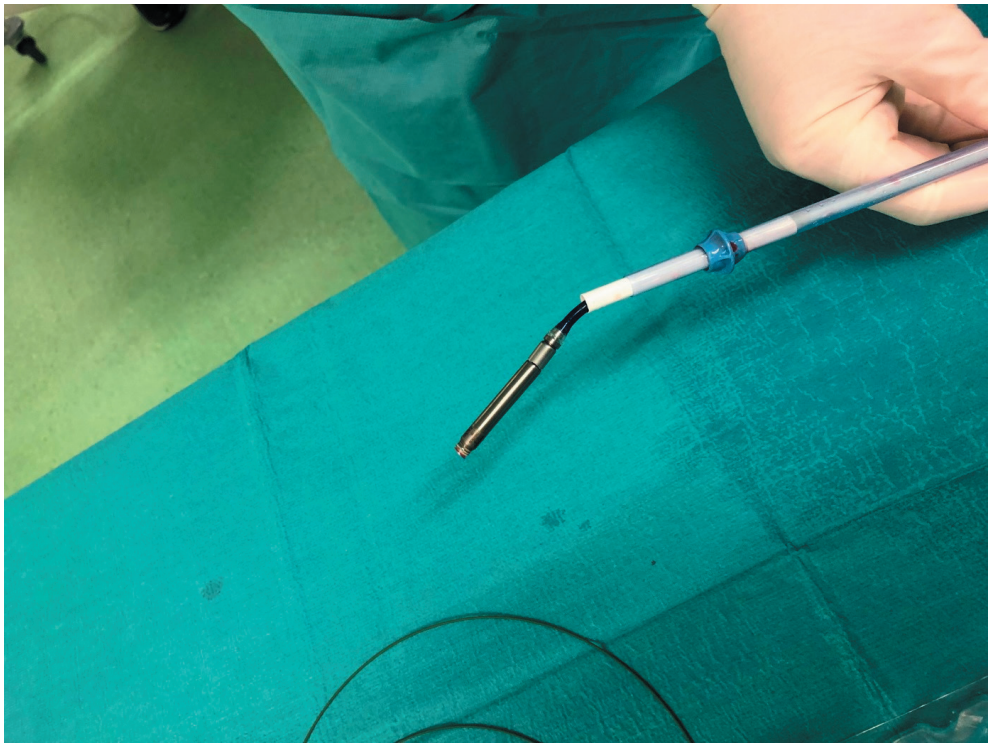

Figure 3. Example of an extracted Nanostim LCP. Successful extraction of a Nanostim LCP due to premature battery depletion. There are no signs of encapsulation or tissue formation around the body of the device. Only minimal fibrous tissue can be seen at the screw-in helix of the Nanostim. Subsequently, a Micra TPS was placed into the right ventricle without complications and with adequate electrical performance parameters.

In an earlier study, retrieval of the Nanostim LCP was successful in 15 of 16 (94%) patients after a mean time from implantation of 240 days(36). The unsuccessful attempt was due to an inaccessible docking button. As no Medical Device Advisory was issued on the Micra TPS, less clinical data on retrieval feasibility are available. In data of the FDA, 7 out of 9 (78%) retrieval attempts were successful. All successful retrievals took place within 6 months after implantation. The unsuccessful attempts were after 229 and 259

days of implantation and were caused by failure of fluoroscopy or inability to dislodge the device(37, 38).

Abandoning the non-functioning device and placing a new leadless pacemaker is an alternative option at end-of-life of the Micra TPS and Nanostim LCP. This option was studied in human cadaver hearts, by implanting multiple Micra TPS in seven hearts following standard procedures after which the heart was dissected (39). The placement of three devices without physical interaction was deemed feasible. Indeed, in a heart of normal dimensions a Micra TPS would occupy approximately 1% of the right ventricular volume (0.8cc in 80±22mL), while three Micra TPSs would occupy 3%(40). Yet, it may be beneficial to limit the number of unnecessary nonfunctioning intracardiac hardware, and therefore mitigate the risk of device-device interference and potential long-term adverse events. To study the effect of multiple leadless pacemakers *in situ* in a contracting heart, two Micra TPS were implanted <1 month in fourteen pigs(41). Four piglets died during the procedure and one died due to an infection. No deterioration of left ventricular function nor tricuspid valve injury was seen after 6 months of follow-up in the remaining pigs. Again, experience in human subjects is limited. In the report on Nanostim LCP revisions in humans after the Medical Device Advisory, it is noted that the Nanostim LCP was abandoned in 115 patients and a new leadless pacemaker or transvenous lead was placed adjacent to the nonfunctioning Nanostim(31). There were no reports of device-device interactions. Regarding the Micra TPS, the FDA reported 7 Micra TPS abandonments. Subsequently, a transvenous pacemaker system was implanted next to a leadless device and no device-device interactions were seen during follow-up.(38)

Expert opinion

Currently, use of leadless pacemaker therapy is limited to patients with a VVI pacing indication. In addition, leadless pacemaker therapy for younger patients requires careful, individual evaluation because optimal end-of-life strategy is yet to be defined. Therefore, studies concerning dual-chamber leadless therapy, leadless cardiac resynchronization therapy, possibilities of leadless devices with improved battery longevity, and alternative pacing modalities are ongoing.

A preclinical proof-of-concept study of leadless dual-chamber pacemaker therapy has been published in which the feasibility is demonstrated *in vitro* and in three pigs *in vivo* (42). Intrabody communication using blood and myocardial tissue was used and was proven to be highly energy-efficient. In addition, the manufacturer of the Nanostim LCP is currently developing a leadless dual-chamber pacemaker system. This system will offer atrial sensing and pacing, AV-synchrony, and ventricular sensing and pacing. This leadless communicating dual-chamber pacing system has the potential to broaden the applicability

of leadless pacing substantially. Furthermore, the feasibility of AV-synchronous pacing in patients with AV block by the Micra TPS using accelerometer-based atrial sensing has been established in the MASS, MASS2, and MARVEL study(43). Moreover, leadless cardiac resynchronization therapy (CRT) using a transvenous pacemaker or implantable cardiac defibrillator (ICD) in combination with a wireless left ventricular endocardial pacing electrode has already been proven to be clinically feasible. The initial WiSE-CRT study was temporarily paused after 17 implantations due to a high number of pericardial tamponade(44). In the SELECT-LV study, the WiSE-CRT system (EBR Systems, Sunnyvale, California) was implanted in 35 patients in whom transvenous CRT had failed(45). The primary endpoint of biventricular pacing at 1 month was achieved in 33 of 34 (97%) patients and 28 of 34 (82%) patients had an improvement of the clinical composite endpoint at 6 months. Device- or procedure-related adverse events occurred in 11 (32%) patients, of which three within 24 hours and additionally 8 up to one month of follow-up. The three acute complications of the WiSE-CRT systems were 1) ventricular fibrillation during implantation of the left ventricular electrode, which resulted in death four days post-implant, 2) embolization of the left ventricular electrode to the left tibial artery, and 3) development of an artery fistula at the femoral access site. The remaining complications included a cerebral vascular accident (n=1), femoral pseudo aneurysm (n=2), pocket hematoma (n=1), and suspected infection at the generator site (n=3). The efficacy and safety profiles were sufficient to start the SOLVE-CRT trial; a randomized, double-blind, sham-controlled study in which 350 patients will be randomized between an active and turned off WiSE-CRT system to evaluate the safety and efficacy of the WiSE-CRT System for cardiac re-synchronization therapy.(46). Further, leadless pacemaker therapy could benefit selected patients requiring ICD therapy in combination with anti-bradycardia or anti-tachycardia pacing, as transvenous ICD therapy is currently the only option for these patients. Modular leadless pacemaker therapy consisting of a communicating leadless pacemaker capable of anti-tachycardia pacing (EMPOWER LCP, Boston Scientific) combined with a subcutaneous ICD (EMBLEM, Boston Scientific) is being studied as an alternative modality(47). Three animal models were studied, with a total of 40 animals, efficacy was proven in terms of ventricular pacing, communication between the devices and anti-tachycardia pacing therapy(48).

A leadless pacemaker system with a self-chargeable battery will provide major improvements in device therapy. Consequently, leadless pacemakers will not be restricted by the life-span of the built-in batteries.(49-52) There are several pacing modalities in development that aim to improve pacemaker longevity. 1) A proof-of-concept energy harvesting leadless pacemaker has been designed, which has not yet been tested *in vivo* .(46) 2) The ability to provide pacing therapy by converting transcutaneous light into electrical energy has been successfully tested in a pre-clinical setting.(47) 3) In another pre-clinical study, a pacing system was developed that provides effective pacemaker

therapy using heart motion.(48) 4) Li and co-workers described an effective novel strategy for directly powering a pacemaker by harvesting the natural energy of a heartbeat in a pre-clinical study.(49) Such energy-harvesting pacemaker systems have the potential to became major game changers and improve effectiveness, applicability, and outcome of pacemaker therapy.

In addition to the rapid progress made in leadless pacemaker therapy, innovative and radically different pacing concepts are currently in development. Firstly, a novel, completely extracardiac temporary pacing system (Atacor Medical, Inc, San Clemente, CA [AtaCor]) placed within the anterior mediastinum has been developed that can deliver bradycardia pacing therapy, while avoiding risks resulting from intravascular, endocardial or epicardial lead and/or device placement.(53) Secondly, in a preclinical study Jordan and coworkers fixated an off-the-shelf pacemaker lead to the atrial appendage and left ventricular free wall within the pericardial space to provide cardiac resynchronization therapy. This innovative pacemaker concept was feasible, yet 1 out of 6 piglets developed a pneumothorax during implantation.(54) Thirdly, John *et al.* described an effective percutaneous placement of an intrapericardial pacemaker lead by using a subxiphoid approach in a pre-clinical setting.(55) Fourthly, the SPACE study established the feasibility of delivering epicardial pacing therapy within the substernal anterior mediastinum in 18 out of 26 patients.(56) Further clinical studies are required to provide more insight on applicability, clinical safety and device performance of these novel pacing modalities.

Leadless pacemaker therapy is a groundbreaking innovation that has introduced a new era of cardiac pacing by mitigating the risks of pacemaker pocket and lead-related complications. The miniaturized intracardiac devices have proven to be feasible with a good short- and intermediate-term safety and efficacy profile, but are generally limited to older patients with an indication for VVI pacing. Studies involving leadless dual-chamber pacing, leadless cardiac resynchronization therapy, modular ICD and leadless pacemaker therapy, and energy-harvesting leadless pacemakers are ongoing and have the potential to supplant conventional lead-based pacemakers for most indications.

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CHAPTER

3

Leadless pacemaker implantation after explantation of infected conventional pacemaker systems: a viable solution?

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Background: Conventional cardiac device infections are increasing in incidence causing significant morbidity and mortality. Leadless pacemaker (LP) therapy may provide new opportunities for the management of pacemaker (PM) infections as it does not require implantation of transvenous leads and a pectoral pocket.

Objective: We sought to evaluate the impact of early and late LP implantation in patients diagnosed with device infection.

Methods: Patients receiving a LP at our center after conventional PM lead extraction due to infection between December 2013 and November 2017 were included.

Results: A total of 17 patients (age 77.4 ± 7.77 years) underwent LP implantation (i.e., 11 Nanostim [Abbott, Chicago, IL, USA] and 6 Micra [Medtronic, Minneapolis, MN, USA]) following successful PM system explantation. In 9 PM-dependent patients a temporary transvenous pacing system was placed as a bridge to permanent LP implantation. Early LP implantation was performed in 6 patients (< 1 week) and in the remaining patients the LP was placed at a later stage (>1 week). All patients experienced no LP infection during a mean follow-up of 16 ± 12 months including 7 patients with a history of recurrent device infections with a mean follow-up of 20 ± 14 months.

Conclusion: Early and late LP placement after infected conventional pacing system explantation was a viable option in our case series. This therapy may provide an alternative strategy, if confirmed by subsequent prospective randomized trials, in the management of device infection, particularly for patients who are PM-dependent or have a history of recurrent device infections.

Abstract word count: 250

Keywords: *Leadless pacemaker therapy, conventional pacemaker therapy, device infection, device and lead extraction, Micra transcatheter pacing system, Nanostim leadless cardiac pacemaker.*

Abstract

Introduction

Conventional pacemakers (PM) have had significant benefit on morbidity and mortality of patients with bradyarrhythmia and are usually well tolerated; however, drastic complications such as PM pocket and/or PM lead associated infection can occur.[1] Device infections are increasing in incidence owing to continually widening indications, frail and older PM recipients and growing numbers of pulse generator replacements. [2,3] PM infections have become a major concern in device management since it is associated with high rates of morbidity and mortality.[4,5]

Conventional PMs with both intravascular and extravascular components are prone to infections primarily involving the pectoral pulse generator and transvenous leads.[1] There is a class I indication to extract all hardware in case of proven or suspected device infection to reduce the risk for life-threatening device-related infective endocarditis and severe systemic infection.[3] In current clinical practice implantation of a new conventional PM is advised after a recovery window in which the infection can be adequately treated to prevent re-infection of the system.[6] The optimal treatment strategy in challenging cases, such as in pacemaker-dependent patients, patients with recurrent device infections or blocked venous access, is subject to debate. In PM dependent patients, a transvenous temporary pacing system serves as a bridge until the new permanent PM can be placed. Conventional temporary pacing requires bed rest and is by itself associated with system infection and sepsis, in addition to other major adverse events such as cardiac perforation, re-intervention, delirium and prolonged hospitalization.[7] In patients in whom the transvenous route is not available, may have required a surgical epicardial approach as the only alternative thus far.

The novel leadless pacemaker (LP) technology, may provide new opportunities for the management of PM infections, specifically in these challenging cases. Intracardiac implantation of the LP without the usage of leads, a pectoral pulse generator or a temporary PM potentially reduces the risk of recurrent infection. Therefore, in this study we report our experience of the impact of early and late LP (i.e., Nanostim [Abbott, Chicago, IL, USA] and Micra [Medtronic, Minneapolis, MN, USA]) implantation after lead extraction in patients with a PM infection.

Methods

Patients receiving a LP device over a 4 year period at the Academic Medical Center Amsterdam (AMC) after conventional PM lead extraction due to infection were included. Demographic data that was obtained included age, sex, body mass index, pacing indication and cardiovascular disease history. This study was approved by the local ethics committee and all participating patients signed informed consent for data collection and publication.

Infection was defined as clinical proven or suspected infection of PM pocket or lead. Transthoracic and transesophageal echocardiography was performed to further confirm the diagnosis of device infection and to evaluate the presence of endocardial or pacing lead involvement. In addition blood samples, lead tips and tissue samples of the device pockets were sent for microbiological analyses. The device and lead explanted procedure was performed in the operating room by an experienced electrophysiologist and cardiothoracic surgeon. All leads were successfully explanted by mechanical traction, surgical intervention or the usage of a laser sheath to vaporize adhesions as it is advanced over the lead. **Figure 1** illustrates examples of an infected PM pocket (Panel A and B) and an extracted infected lead (Panel C). In 9 PM dependent patients, a temporary pacing lead was implanted as a bridge to LP implantation. Two strategies were used: early LP implantation (2-7 days post-explantation), despite potential on-going infection according to elevated C-reactive protein (CRP; i.e., more than 10 mg/L) and white blood count or delayed LP placement (>1 week) after clinical signs of ongoing infection were gone. The strategy for re-implantation with a LP was determined in a multidisciplinary team. Early implantation was performed in pacemaker dependent patients or patients with normal levels of CRP and leucocytes.

Two types of LPs were implanted in the current study. The LPs are cylindrical intracardiac devices, however there are differences in design: the Nanostim is 42mm long and 6mm in diameter, whereas the Micra measures 26mm in length and 6.7mm in diameter.[8,9] LP implantation was performed under fluoroscopy in the catheterization laboratory by an experienced electrophysiologist. An introducer sheath (27Fr outer diameter (OD) for the Micra and 21Fr OD for the Nanostim) was percutaneously placed in the femoral vein to deliver the device through the vena cava inferior towards the right ventricular myocardium using a steerable catheter. The Nanostim device is fixated in the cardiac tissue with a helix at its distal end and by rotating the device. The Micra device is anchored into the ventricular myocardium by 4 Nitinol tines which dig into the myocardium when the device is pushed out of the catheter. Procedural (i.e., LP implant duration, number of deployments, adverse events) and device data (i.e., pacing capture threshold, R-wave amplitude and pacing impedance) were prospectively collected.

Patients were followed in the setting of regular care visits at our center. At our center the routine follow-up for LP therapy consists of follow-up visits at 2 weeks, 3 months, 6 months, 12-months and every 6 months thereafter. Echocardiographic evaluation was performed during follow-up visits and laboratory tests were performed if indicated.

Data are presented as numbers and percentages, mean ± standard deviation and median (interquartile range). All statistical analyses were performed using IBM SPSS Statistics for Windows (or Macintosh), Version 24.0 Armonk, NY, IBM Corp.

Results

There were 17 explantations and re-implantation procedures at our tertiary referral center between December 2013 and November 2017. The infected transvenous PM systems included: a dual-chamber (DDD) pacing system in 7 patients, a single-chamber (VVI) pacing system in 9 patients, and in 1 patient a cardiac resynchronization therapy (CRT) device. Seven patients had a history of device and lead extraction due to infection. **Table 1** summarizes the baseline characteristics of the total study population.

Table 1. Baseline characteristics

	(n=17)
Age, years	77.4 ± 7.77
Male, n (%)	16 (94%)
BMI (kg/m^2)	23.8 ± 2.463
Pacing Indication, n (%)	
Bradycardia associated with persistent or permanent atrial tachyarrhythmia	10 (58.8%)
Sinus node dysfunction	1 (5.88%)
Atrioventricular block	6 (47.1%)
Cardiovascular Disease History, n (%)	
Pacemaker infection and extraction	7 (41.2%)
Congestive heart failure	2 (11.8%)
Coronary artery disease	8 (47.1%)
Hypertension	7 (41.2%)
Myocardial infarction	8 (47.1%)
Pulmonary hypertension	0 (0%)
Tricuspid valve dysfunction	3 (17.6%)
Cardiomyopathy	3 (17.6%)
Other Comorbidities, n (%)	
COPD	4 (23.5%)
Diabetes	6 (35.3%)
Renal dysfunction	3 (17.6%)
CVA	3 (17.6%)
Primary transvenous pacemaker, n (%)	
VVI	9 (53%)
DDD	7 (41%)
CRT	1 (5.8%)
Microorganisms identified by bloodculture, n (%)	
Staphylococcus aureus	7 (41.2%)
Other gram-positive cocci	3 (17.6%)
Negative blood culture	4 (23.5%)
Unknown blood culture	3 (17.6%)
Type of pacemaker associated infection, n (%)	
Pocket infection only	7 (41.2%)
Pocket and lead infection	7 (41.2%)
Lead infection only	3 (17.6%)
Leadless pacemaker	
Nanostim LP, n (%)	11 (65%)
Micra TPS, n (%)	6 (35%)

BMI; body mass index, COPD; chronic obstructive pulmonary disease, CRT; cardiac resynchronization therapy; CVA; cerebellar vascular accident, DDD; dual-chamber, LP; lead pacemaker, TPS; transcatheter pacing system, VVI; single-chamber

All 17 patients had a class I indication for complete removal of the conventional pacing system.[10] The presentation of the device infection varied in the current patient cohort. Fourteen patients were diagnosed with a pocket-infection identified by typical local inflammatory changes such as erythema, swelling and/or erosion of skin, but different in severity. **(Figure 1, panel B)** Of these, 7 were diagnosed with a pocket infection only, whereas in the other 7 transesophageal and transthoracic echocardiography revealed lead involvement. In the remaining 3 patients without evidence for a pocket infection, transesophageal and transthoracic echocardiographic evaluation demonstrated lead vegetation. **(Figure 2)** In 10 patients, blood cultures were positive for Staphylococcus aureus (n=7) or other Gram-positive cocci (n=3), whereas in 4 patients, despite typical signs of PM infection, blood cultures were negative, or unknown (n=3).

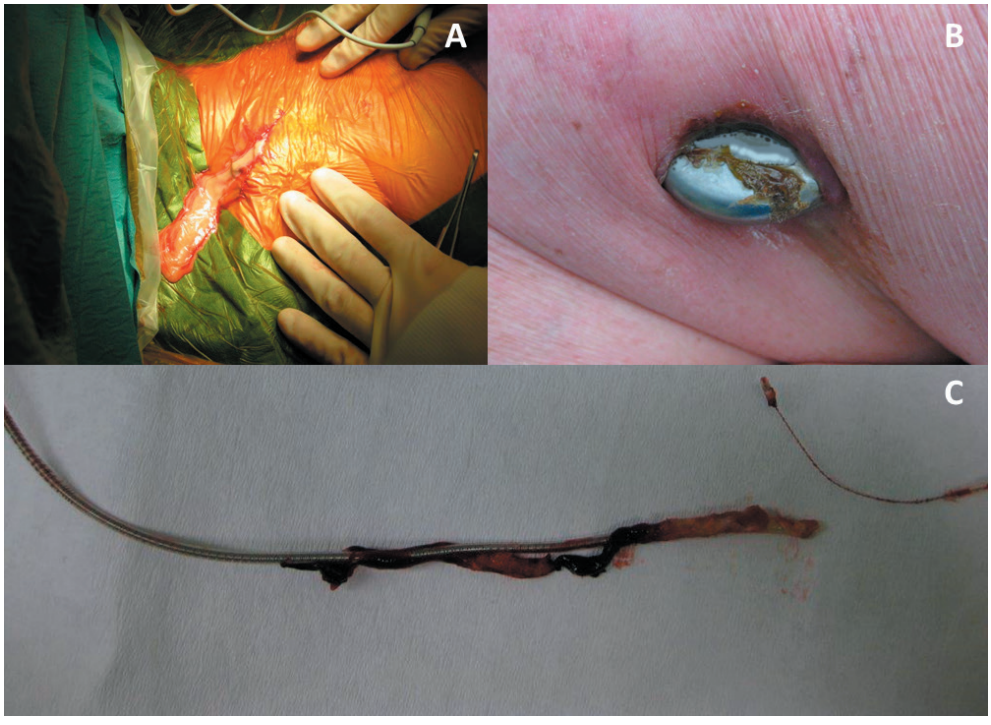

Figure 1. ***Panel A****: Pacemaker pocket infection with extensive pus.* ***Panel B:*** *Perforated pulse generator.* ***Panel C****: Explanted lead with adherent fibrotic tissue.*

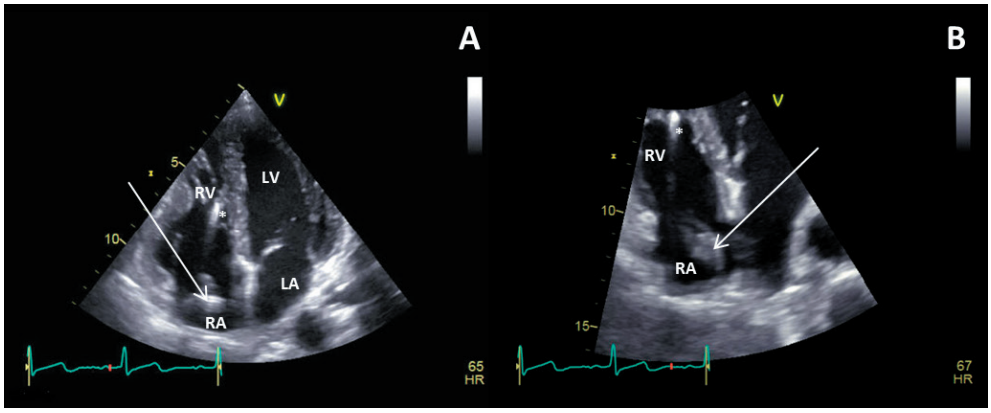

Figure 2. Transthoracic echocardiographic evaluation of a patient with lead endocarditis. Vegetation on the atrial lead (arrow). Right ventricular lead (asterisk).

In this cohort, 6 Micra and 11 Nanostim implantations were completed without complications and with acceptable electrical parameters. In 6 patients, early LP implantation (2-7 days post-explantation) was performed. Out of these, 3 patients had an elevated CRP of 11 mg/L, 51 mg/L, and 82 mg/L at the time of implant. In the remaining 11 patients, delayed LP placement (>1 week) was performed after clinical signs of ongoing infection were gone. The device parameters at implant and follow-up visits are listed in **Figure 3.** Successful implantation within a single deployment of the device was achieved in 12 patients. In 4 patients, of whom 2 underwent Nanostim and 2 Micra implantation, 2 deployments were needed before reaching adequate electrical parameters. In 1 patient 4 deployments of the Micra were required before obtaining adequate pacing capture thresholds and R-wave amplitudes. The mean total LP implantation time (i.e., time from access until removal of the introducer) was 38.7 ± 16.8 minutes. There was 1 patient who experienced an access site complication 1 day post-implant (i.e., arteriovenous fistula), but this did not result in prolonged hospitalization. All patients were discharged 1-3 days after the LP procedure with a decreasing CRP or negative blood cultures and no clinical signs of infection. **Figure 4** and **Table 2** demonstrate the duration from initial conventional device implantation to first (and recurrent) device infection resulting in explantation before LP implantation. There were no LP device infections up to 42 months with a mean follow-up of 16 ± 12 months (**Figure 4)** according to available echocardiography, laboratory tests and absence of clinical symptoms. There were no instances of PM-syndrome in the current cohort, despite the fact that 7 patients had a DDD-pacing indication. There were 4 patients who died during follow-up, all non-related to recurrent device infection or LP therapy. Two patients died from multi organ failure syndrome in sepsis both originating from a necrotic foot ulcer. Metastatic cancer accounted for the 2 remaining deaths. In 1 PM-dependent patient, the Nanostim device was replaced by a Micra due to battery malfunction 10 months after implantation. Histopathological examination of the extracted Nanostim showed minimal adherent fibrous tissue at the helix and no signs of recurrent infection.

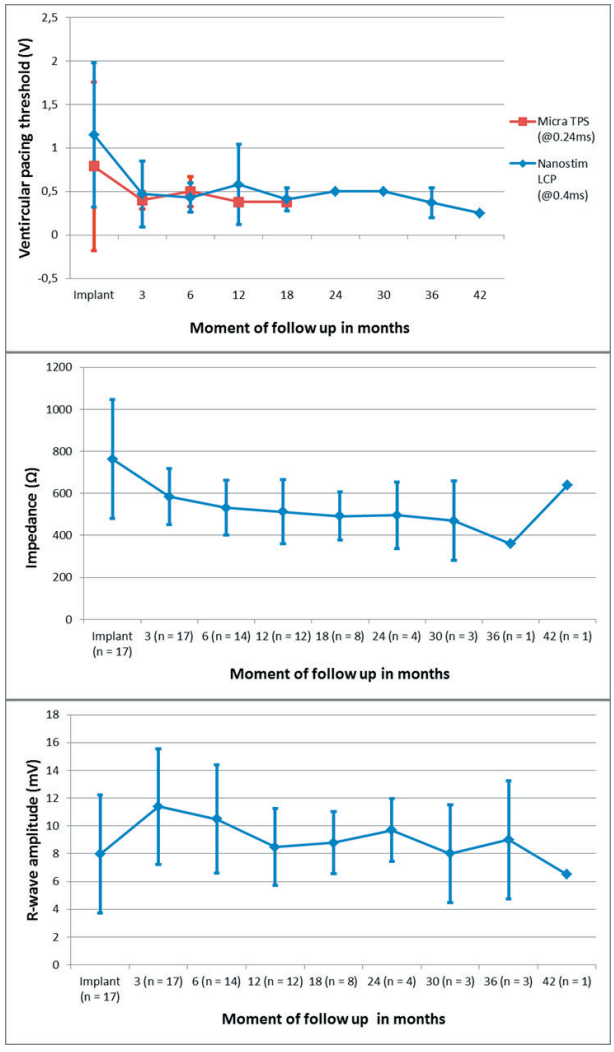

Figure 3. Device parameters (mean + SD) of the LP at implant and follow-up visits.

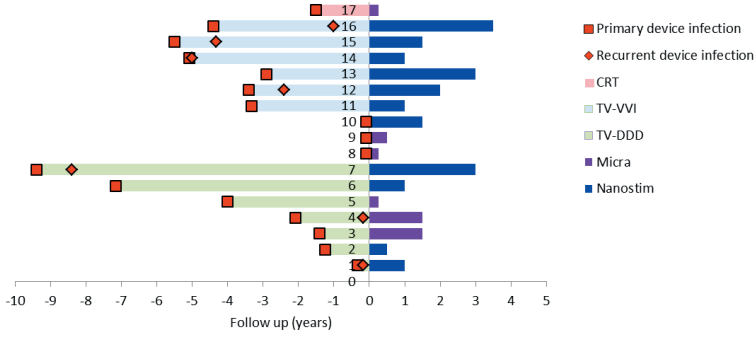

Figure 4. A swimmer plot illustrating the duration from initial conventional device implantation to first and in 7 patients recurrent pacemaker system infection resulting in device extraction. All patients experienced no leadless pacemaker infection during a mean follow-up of 16 ± 12 months.

Table 2. Duration from initial conventional device implantation to first (and recurrent) device infection

Patient	Primary pacemaker, implant year	Time to infection +extraction (months)	Second pacemaker, implant year	Time to recurrent infection+ extraction (months)	Third pacemaker, implant year	Re-infection LP therapy?	Follow-up post-LP implant (months)
1	TV-DDD, 2014	17	Micra, 2016	N/A	N/A	No	18
2	TV-VVI, 2016	1	Micra, 2016	N/A	N/A	No	3
3	TV-DDD, 2013	48	Micra, 2017	N/A	N/A	No	3
4	TV-VVI, 2017	1	Micra, 2017	N/A	N/A	No	6
5	TV-CRT-D, 2016	18	Micra, 2017	N/A	N/A	No	3
6	TV-DDD, 2015	2	TV-DDD, 2015	23	Micra, 2017	No	18
7	TV-VVI, 2007	52	TV-VVI, 2011	14	Nanostim, 2013	No	18
8	TV-VVI, 2009	12	TV-VVI, 2010	41	Nanostim, 2013	No	42
9	TV-DDD, 2012	15	Nanostim, 2014	N/A	N/A	No	6
10	TV-VVI, 2011	35	Nanostim, 2014	N/A	N/A	No	36
11	TV-DDD, 2005	101	TV-DDD, 2013	12	Nanostim, 2015	No	36
12	TV-VVI, 2011	29	TV-VVI, 2013	12	Nanostim, 2015	No	24
13	TV-VVI, 2016	1	Nanostim, 2016	N/A	N/A	No	18
14	TV-DDD, 2009	86	Nanostim, 2016	N/A	N/A	No	12
15	TV-VVI, 2011	60	TV-VVI, 2016	1	Nanostim, 2016	No	12
16	TV-DDD, 2016	2	TV-DDD, 2016	2	Nanostim, 2016	No	12
17	TV-VVI, 2013	40	Nanostim. 2016	N/A	N/A	No	12

CRT-D cardiac resynchronization therapy defibrillator; DDD dual chamber; LP leadless pacemaker; N/A not applicable; TV transvenous; VVI single-chamber

Discussion

In the current study, early and late Nanostim and Micra placement was examined after successful removal of the infected transvenous pacemaker system. The LP was implanted without serious complications in all patients after successful device system removal. There were no cases of recurrent device infection in the 10 patients diagnosed with systemic and 7 with pocket infection during a mean follow-up of 16 ± 12 months. Seven patients with a history of recurrent device infections experienced no LP infection with a mean follow-up of 20 ± 12 months. These findings suggest that in selected patients early LP implantation, even in ongoing infection, is safe and feasible. In addition, delayed LP implantation after an infection recovery window may be considered in patients with a history of multiple device infections or blocked venous access.

The incidence of device infections is increasing due to a world-wide expansion of device implantations and growing number of revision procedures associated with a 2 to 5-fold higher risk for infection.[11-13] The risk of device infection is estimated at approximately 1- 2%.[14-17] Device infections can manifest as a local infection of the pectoral pocket or can involve the intravascular leads and endocardium. Device infections account for 10% of endocarditis cases. [2,3] Device infections are potentially fatal and virtually always necessitate complete PM system removal.[6] Reported mortality rates associated with device infection are inconsistent, but range between 0 to 35%.[6]

To our knowledge, we present the largest study thus far with the longest follow-up evaluating safety and feasibility of LP therapy following conventional PM infection. In the two large prospective multicenter Micra and Nanostim trials, patients with an history for device explantations were excluded.[8,9] We showed that implantation of the LP was feasible and safe in all patients according to a short procedure time, acceptable electrical parameters, number of LP deployments, absence of serious complications and early post-procedural discharge. The current results are in line with previously published data in that there were no instances of LP infection.[18] There are differences between the aforementioned and the present study that merit emphasis. Kypta and co-workers evaluated the safety of early Micra implantation in 6 patients post-lead explantation, while we used both clinically available LPs: the Micra and Nanostim in 6 and 11 patients, respectively. They concluded that all patients stayed free of infection during a follow-up period of maximum 3 months, whereas in this study the follow-up period was much longer with a mean of 16 months and a maximum of 42 months. Kypta *et al.* demonstrated that in 2 patients implantation of a Micra just before the conventional PM lead extraction during the same procedure, is feasible.

Recommendations and perspectives

Options and strategies for device management in PM infection should be considered carefully and should be tailored to a patients specific clinical situation. The possibility of a less complex leadless VVI device associated with lower infection risk should be weighed against potential benefits of a more complex DDD system. The use of a small intracardiac LP eliminates pocket infection, lead complications and the necessity of infection-prone pectoral generator replacements. In theory, the occurrence of LP encapsulation may decrease the risk for device infection on the long-term since the device is sealed off from bacteria. On the other hand, one may argue that reduced blood circulation in fibrotic tissue may enhance bacterial colonization. Advocates for the implantation of a more complex DDD system may argument that these patients are more prone to the development of PM syndrome caused by the leadless ventricular PM. However, in our patient cohort none of the patients developed PM syndrome, despite the fact that a DDD PM was indicated in 7 patients. Current guidelines recommend to treat and cure ongoing infections before implantation of a new PM system, because patients with a fever <24 hours prior to implant have a 5.8 times higher risk for infection, but specific recommendations on a recovery window are not made.[19] However, this can be challenging in PM dependency since they require acute pacing therapy. Conventional temporary pacing leads can be implanted as a bridge to permanent PM implantation. Yet, these temporary transvenous lead are associated with maintaining and recurrence of device infections (odds ratio: 2.5).[19,20] In addition, patients with a temporary pacing lead are mandated bed rest and are at risk for cardiac perforation, delirium and prolonged hospitalization.[7] Therefore, optimal timing and treatment in these PM dependent patients remains an unsettled concern. We showed that in our case series, early LP implant was a safe alternative in these patients. In the current study, all patients implanted with a LP were discharged within 3 days post-implant. Therefore, this strategy, especially when utilizing early LP implantation, has the potential to improve the economical and logistic burden associated with device infections and extractions by shortening hospital admissions. Prospective randomized data on LP therapy in the management of device infections are required to determine if our suggested strategy contributes to more effective treatment strategies and better outcome.

Limitations

This current analysis is limited by its retrospective nature. This study is limited by a small number of patients. Although we used available echocardiography, blood cultures and clinical symptoms to identify device infection, the diagnosis of re-infection of the LP may have been missed in some patients. It is also possible that despite relatively long follow-up in the majority of patients of this series, LP infection may occur at a later stage.

Conclusion

Early and late LP placement after conventional cardiac device removal due to infection showed to be a viable option in our case series. Therefore, this therapy may provide a safe solution in the management of device infection, if confirmed by subsequent prospective randomized trials or follow-up studies, particularly for patients who are PM-dependent or prone to recurrent infection.

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CHAPTER

Health-Related Quality of Life Impact of a Transcatheter Pacing System

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Background Transcatheter pacing systems (TPS) provide a novel, minimally invasive approach in which a miniaturized, leadless pacemaker (PM) is transfemorally implanted in the right ventricle. We evaluated the Health Related Quality of Life (HRQoL) impact, patient satisfaction and activity restrictions following TPS in a large prospective multicenter clinical trial.

Methods and Results Patients who underwent a Micra TPS implantation between December 2013 and May 2015 were included. HRQoL impact was evaluated using the SF-36 questionnaire at baseline, 3 and 12 months. Patient satisfaction was assessed using a 3-item questionnaire determining recovery, activity level, and esthetic appearance at 3 months. Implanting physicians compared the patient activity restrictions for TPS to traditional PM therapy.

A total of 720 patients were implanted with a TPS (76 ± 11 years; 59% male). Of these patients, 702 (98%), 681 (95%) and 635 (88%) completed the SF-36 at baseline, 3 and 12 months, respectively. Improvements were observed at 3 and 12 months in all SF-36 domains and all attained statistical significance. Of 693 patients who completed the patient satisfaction questionnaire, 96%, 91%, 74% were (very) satisfied with their esthetic appearance, recovery, and level of activity, respectively. TPS discharge instructions were rated less restrictive in 49%, equally restrictive in 47%, and more restrictive in 4% of cases compared to traditional PM systems.

Conclusions TPS resulted in post-implant HRQoL improvements at 3 and 12 months, and high levels of patient satisfaction at 3 months. Further, TPS was associated with less activity restrictions compared to traditional PM systems.

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Abstract

Introduction

Cardiac pacemakers (PM) are the preferred and widely used therapy to decrease morbidity and mortality in patients with various symptomatic bradyarrhythmias.[1-4] PM therapy has evolved substantially over the past years. The recently introduced Micra Transcather Pacing System (TPS) provides a novel approach to pacing therapy, in which a leadless PM is completely implanted in the right ventricle through a minimally invasive procedure. Currently TPS is implanted only in patients who have an indication for single chamber ventricular (VVIR) pacing.[5] The TPS may have significant clinical benefits to the conventional design of transvenous PM since it circumvents the use of transvenous leads and subcutaneous pocket of the pulse generator, which are the main sources of serious peri- and postprocedural complications (e.g. hematoma, skin erosion, pocket infection, pneumothorax, cardiac tamponade and lead dislodgment).[6-8]

Health Related Quality of Life (HRQoL) impact is considered an important validated metric to measure patient clinical status and quality of life and therefore represents a cornerstone in clinical treatment effectiveness.[9] HRQoL improvement following PM implantation has been shown in various transvenous PM trials. [10-14] The minimally invasive TPS procedure could provide additional benefits that may enhance improvement in HRQoL compared to the conventional transvenous PM, such as cosmetic benefit, earlier hospital discharge, fewer complications and re-hospitalization.[5] In addition, TPS overcomes the need for activity restrictions that are required for the arm ipsilateral to the PM implant site following conventional PM surgery required to prevent lead dislodgement, and therefore may improve patient satisfaction and HRQoL. [5, 15]

With the increasing number of patients in whom the TPS is implanted, monitoring late effects on HRQoL, patient clinical status and activity restrictions becomes increasingly important. Yet to date, the effect of TPS on the aforementioned essential clinical outcomes has not been evaluated. Therefore, we aimed to assess the HRQoL impact, patient satisfaction and activity restrictions following TPS in a large prospective multicenter clinical trial.

Methods

Micra Study cohort

The rationale and design of the Micra TPS study has been described previously.[16] In brief, it was a single-arm prospective multicenter clinical trial enrolling 726 patients, with a class I or II guideline indication for VVIR pacing, in 56 centers and 19 countries between December 2013 and May 2015.[15,16] Implanted patients were followed for a minimum of 12 months. The aim of this study was to assess the safety and performance

of the Micra transcatheter pacing system (TPS), a miniaturized intracardiac PM which is implanted via a percutaneous transfemoral route. The study protocol was approved by the Institutional Review Boards from all participating centers and complied with the declaration of Helsinki.

Health Related Quality of Life

Multidimensional HRQoL was assessed with the Medical Outcomes Study 36-Item Short-Form (SF-36) General Health Survey [17,18], which incorporates two composite scales: the Physical Component Scale and the Mental Component Scale. These scales are derived from eight domains: physical functioning, social functioning, role physical, role emotional, mental health, bodily pain, vitality, and general health. The domains that relate most strongly to the Physical Component Scale are physical functioning, role physical and bodily pain, whereas, mental health, role emotional and social functioning most strongly relate to the Mental Component Scale. The domains of vitality and general health are associated with both component scales. For each of the eight domains an aggregate percentage score is produced, and are ranked on a scale from 0 (worst possible level of functioning) to 100 (highest possible level of functioning). [19] Validated SF-36 questionnaires were translated in the various native languages for each participating center. SF-36 questionnaires were obtained at three serial time points: at baseline (pre-implant), 3 months, and 12 months post-implant.

Patient satisfaction questionnaire

A non-validated 3-item questionnaire was used to assess patient satisfaction following TPS implant regarding three domains: 1) recovery, 2) esthetic appearance, and 3) level of activity. The three domains were scored using a 5-item scale (very dissatisfied, dissatisfied, neutral, satisfied, very satisfied). This questionnaire was obtained at the follow-up visit 3 months after implant.

Activity restrictions

All implanting physicians were asked to complete a questionnaire describing activity restrictions provided to the patient at the time of discharge, and compared to activity restrictions provided after a transvenous PM implant. The activity restrictions were scored less restrictive, equally restrictive, or more restrictive compared to traditional PM systems. (Supplementary File 1)

Statistical methods

For baseline characteristics, mean and standard deviation were reported for continuous variables, and frequency and percentage were reported for categorical variables. Responses to questionnaires were summarized using frequencies and percentages. In order to enable comparisons with the general population mean, SF-36 scores from summary component

scores and individual domains were transformed into standardized T-scores and normed to a mean of 50 and a standard deviation of 10. A summary component score or domain less than 50 indicated HRQoL that was worse in the studied population compared to the general population. Normative values for a US population were used in the calculation of the standardized scores as similar values were not available for most countries. Changes in HRQoL scores from baseline to 3 months and 12 months were assessed using paired t-test. P-values < 0.05 were considered statistically significant.

A multivariate regression analysis was performed to identify factors which might be associated with HRQoL improvement from baseline to 12 months. The factors that were explored included: age, gender, baseline HRQoL score, diabetes, renal dysfunction, chronic obstructive pulmonary disease (COPD), hypertension, congestive heart failure, coronary artery disease, cardiomyopathy, pulmonary hypertension, tricuspid valve dysfunction, number of comorbidities, and occurrence of serious adverse events within 12 months. The final model was selected using a backward elimination method keeping age, gender and all factors with a p-value < 0.1 in the model. All analyses were conducted using SAS software version 9.4 (SAS Institute).

Results

Patients

The Micra TPS was successfully implanted in 720 (99.2%) out of the 726 patients with implant attempt. The baseline patient characteristics are displayed in **Table 1**. Of these patients, 702 (98%), 681 (95%), and 635 (88%) completed the SF-36 questionnaire at baseline, 3 month and 12 months, respectively. Of the 85 patients who did not complete the SF-36 questionnaire at 12 months, 52 died, 7 discontinued the study and 26 patients did not (fully) complete the SF-36 questionnaire. There was no death occurred as a result of complications from the device. There was one procedure-related death with the diagnosis of metabolic acidosis; all remaining 51 deaths (including 8 due to heart failure) were adjudicated by the independent Clinical Events Committee as not related to the Micra system or procedure.

Table 1. Baseline patient characteristics

Subject Characteristics	(n=720)
Age, y	75.8 ± 11.0
Male, n (%)	425 (59%)
Pacing Indication, n (%)	
Bradycardia associated with persistent or permanent atrial tachyarrhythmia	460 (63.9%)
Sinus node dysfunction	125 (17.4%)
Atrioventricular block	108 (15.0%)
Other	27 (3.8%)
Height (cm)	168.8 ± 10.7
Weight (kg)	79.0 ± 18.4
BMI	27.6 ± 5.3
Cardiovascular Disease History, n (%)	
Cardiomyopathy	79 (11.0%)
Congestive heart failure	129 (17.9%)
Coronary artery disease	201 (27.9%)
Hypertension	565 (78.5%)
Myocardial infarction	76 (10.6%)
Pulmonary hypertension	79 (11.0%)
Tricuspid valve dysfunction	187 (26.0%)
Other Comorbidities, n (%)	
COPD	91 (12.6%)
Diabetes	205 (28.5%)
Renal dysfunction	147 (20.4%)
Chronic Lung Disease	212 (29.4%)

HRQoL main outcomes

SF-36 Physical Component Scale and Mental Component Scale were both below the general population mean of 50 at baseline (mean Physical Component Scale 36.3 ± 9.0; mean Mental Component Scale 47.3 ± 12.5). Both Physical Component Scale and Mental Component Scale improved 3 months post-TPS implant (mean Physical Component Scale 38.7 ± 9.1; mean Mental Component Scale 50.9 ± 11.6; $p < 0.001$) and this increase was sustained through 12 months of follow-up (mean PCS 38.6 ± 9.4; mean MCS 50.7 ± 12.2; $p < 0.001$ compared to baseline; **Figure 1**)**.** Unlike the Mental Component Scale, the Physical Component Scale remained below the general population mean at 3 and 12 months. Mean baseline SF-36 scores for five of the eight individual domains were above the general population mean, except for role physical (49.1 ± 30.1); vitality (48.4 ± 23.1) and bodily pain (40.4 ± 11.8). An increase in SF-36 scores was observed in all individual SF-36 domains from baseline to 3 and 12 months ($p < 0.05$; **Figure 2**). The largest SF-36 improvement was observed in the role physical domain (11.2 point increase at 12 months), while the lowest improvement observed in the bodily pain domain (1.3 point increase at 12 months). Bodily pain was the only individual domain that remained below the general population mean at 3 and 12 months post-TPS implant.

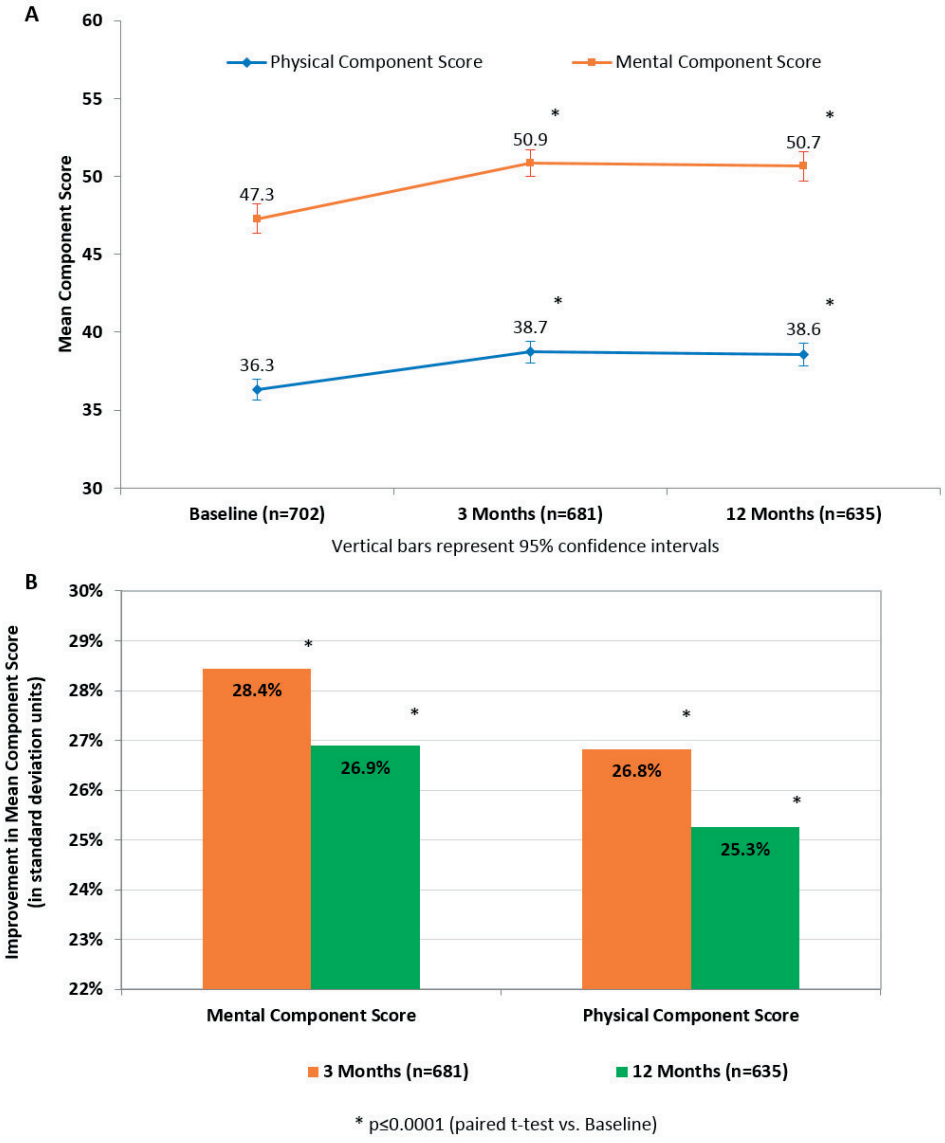


Figure 1. SF-36 aggregate score results at baseline, 3-months and 12-months after TPS implant

Panel A. In this figure the PCS and MCS aggregate results are displayed at baseline, 3-months and 12-months of follow-up after TPS implant. PCS and MCS scores have increased significantly from baseline to 3 and 12 months, respectively (p value ≤ 0.0001, denoted with *). The vertical bars represent the 95% confidence intervals for each aggregate score.

Panel B. In this figure the relative change in percentage of the baseline for the PCS and MCS aggregate scores are presented.

A multivariate regression analysis identified increasing age (-0.17 points per year age-increase, $p < 0.001$), patients with renal dysfunction at baseline (-1.57 points, $p = 0.047$) and the occurrence of a serious adverse event (-2.03 points, $p = 0.001$) as independent predictors for worse HRQoL outcome on the Physical Component Scale, and patients with cardiomyopathy (-3.24 points, $p = 0.037$) for worse HRQoL on the Mental Component Scale (**Table 2**). Conversely, renal dysfunction (+2.45 points, $p = 0.045$) was identified as a predictor for better HRQoL on the Mental Component Scale.

Table 2. Multivariate regression modeling for PCS and MCS

Multivariate Analysis (n=623)			
Change in Physical Component Score (from baseline to 12 months)			
Factor	**Effect Estimate**	**95% CI**	**P-value**
Age	-0.17	(-0.22, -0.12)	<0.0001
PCS at Baseline	-0.43	(-0.50, -0.37)	<0.0001
Renal Dysfunction	-1.57	(-3.2, -0.02)	0.047
Serious Adverse Event	-2.03	(-3.24, -0.83)	0.001
Change in Mental Component Score (from baseline to 12 months)			
Factor	**Effect Estimate**	**95% CI**	**P-value**
MCS at Baseline	-0.60	(-0.67, -0.53)	<0.0001
Renal Dysfunction	2.45	(0.06, 4.85)	0.045
Diabetes	-1.95	(-3.94, 0.04)	0.055
Cardiomyopathy	-3.24	(-6.28, -0.20)	0.037

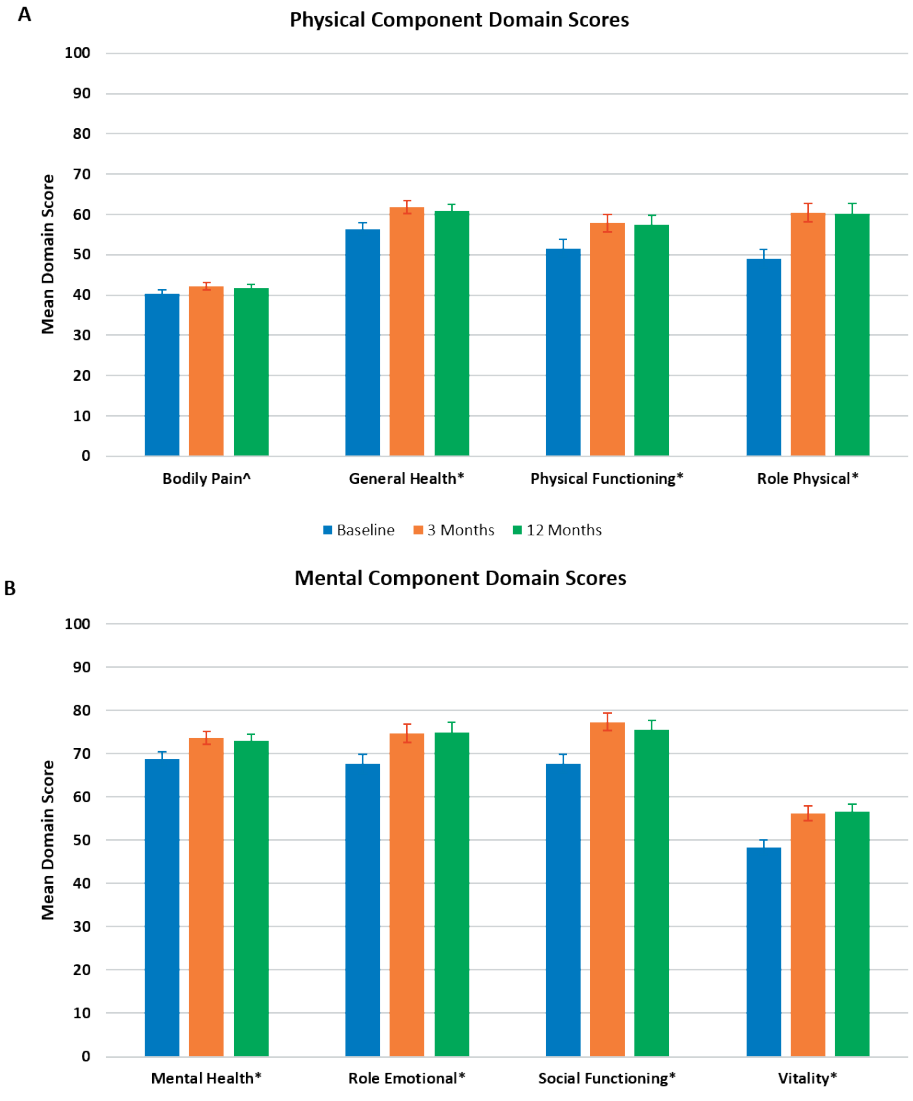


Figure 2. SF-36 domain score results at baseline, 3-months and 12-months after TPS implant

All eight individual SF-36 domains were improved from baseline to 3 months and 12 months after TPS implant, respectively. The mean scores (mean ± standard deviation) for each individual domains at baseline, 3-months, and 12 months were, respectively: Panel A: PF: 51.6 ± 29.4, 57.8 ± 29.5, and 57.5 ± 30.5; RP: 49.1 ± 30.1, 60.4 ± 30.5, and 60.3 ± 30.8; BP: 40.4 ± 11.7, 42.2 ± 11.3, and 41.7 ± 11.3; GH: 56.4 ± 20.3, 61.9 ± 21.2, and 60.8 ± 21.1. Panel B: VT: 48.4 ± 23.2, 56.3 ± 22.4, and 56.7 ± 22.5; SF: 67.7 ± 29.4, 77.4 ± 26.2, and 75.6 ± 27.9; RE: 67.7 ± 30.7, 74.8 ± 28.3, and 75.0 ± 28.6; and MH: 68.9 ± 20.9, 73.6 ± 19.7, and 73.1 ± 20.1. The vertical bars represent the 95% confidence intervals for each individual domain score.

Patient satisfaction

Of the 720 patients, 693 (96%) completed the 3-item patient satisfaction questionnaire at the 3-month follow-up visit. Results of this questionnaire are displayed in **Figure 3**. Majority of patients who completed the questionnaire were either satisfied or very satisfied with their recovery (91%), their esthetic appearance (96%) and their level of activity after implant (74%).

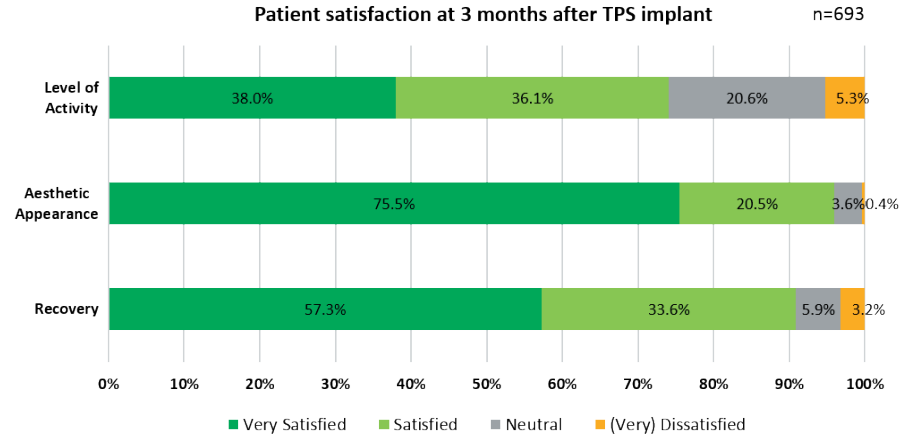


Figure 3. Patient satisfaction at 3 months after TPS implant

In this figure the results are presented from the 3-item questionnaire assessing self-reported patient satisfaction with regard to recovery, esthetic appearance and level of activity.

Activity restrictions

In all but one case, (n=719/720, 99.8%) the implanting physician rated the TPS patient activity restrictions as part of the patient discharge instructions compared to conventional PM systems. These activity restrictions were rated less restrictive, equally restrictive, and more restrictive in 49%, 47% and 4% of cases, respectively, for TPS compared to conventional PM systems. "Longer requested bed rest period" was indicated as the main reason (n=22/30, 73%) for rating the TPS activity restrictions more restrictive than with a conventional PM.

Discussion

We report the largest contemporary single-chamber PM cohort in which HRQoL is studied after TPS implant. Our study represents the only study thus far to describe HRQoL outcomes in patients implanted with leadless PMs, up to 12 months post-implant. TPS resulted in substantial improvements in the physical and mental component scores as well as individual domains of the SF-36 measure. We further observed that TPS resulted in high levels of patient satisfaction in terms of recovery, esthetic appearance of the implant,

and the level of activity at 3 months post-implant compared to baseline. In addition, the majority of implanting physicians considered the impact of TPS on activity restrictions as less restrictive or equally restrictive compared to the conventional PM system.

Health Related Quality of Life

The impact of PM therapy on patient symptoms and HRQOL can provide a holistic picture of treatment effectiveness. The TPS patient cohort was characterized by baseline Physical Component Scale and Mental Component Scale scores that fell below the general population mean suggesting a significant disease burden in this patient population. Following TPS implantation, mean Physical Component Scale and Mental Component Scale scores improved at 3 and 12 months, consistent with trends in HRQoL improvement reported in a traditional PM study that applied the same norm-based scoring approach. [10] Among individual domains, the greatest improvement was observed on role physical scores. One possible explanation is that because PMs alleviate symptoms of bradycardia such as syncope, dyspnea and palpitations this may positively impact normal physical functioning. Bodily pain scores showed the least improvement from baseline; a finding that was not unexpected as PMs do not generally alleviate pain.

Younger patients had greater improvement in HRQoL scores compared to older patients in terms of the aggregate physical function, which is also in line with previous observations in transvenous PM cohorts.[10] The occurrence of serious adverse events adversely affected physical HRQoL. Most of these serious adverse events were not related to the Micra procedure or system, but reflections of patients' comorbidities or natural disease progression. In a post-hoc comparison to a matched historical transvenous control cohort, Reynolds *et al.* observed significantly fewer complications, system revisions, and hospitalizations following TPS.[5] Other predictors for worse HRQoL were preexisting co-morbidities such as renal dysfunction and cardiomyopathy. This could reflect the fact that these are generally sicker patients. However, renal dysfunction was also associated with better mental HRQoL outcome, which is not clearly understood and might be a spurious signal due to chance. Of note, the potential harm of implanting a single-chamber pacing device in patients with CHF or baseline cardiomyopathy should be taken into consideration since cardiomyopathy was a predictor for worse HRQoL on the Mental Component Scale.

Direct comparison of HRQoL impact between TPS and conventional PM was not feasible due to a single-arm clinical study design. However, there were some notable observations made when we compared TPS HRQOL outcomes with data from 2 conventional PM trials - the Mode Selection Trial (MOST) and the Pace Selection in the Elderly (PASE) study. [10, 13] Firstly, the baseline TPS bodily pain score was considerably lower (by 20 points or more) than conventional PM patients' bodily pain scores (**Figure 4, Panel A**). Secondly, while TPS resulted in improvements in all domains of the SF-36 at 3 and 12 months, the

magnitude of improvement in role physical was lower than in conventional PM patients. (**Figure 4, Panel B, C**). We conjecture that the lower magnitude of improvement in role physical scores in TPS patients could be attributed to a low bodily pain score which did not improve with pacing therapy, thus limiting patients' abilities to perform physical roles. Nonetheless, TPS performed better than conventional VVI-R PM on the general health score which showed little or no improvement for conventional VVI-R PM at 3 and 12 months**.** Similar trends in HRQoL scores were reported in FOLLOWPACE, a prospective observational study of traditional PM outcomes in a Dutch population.[20]

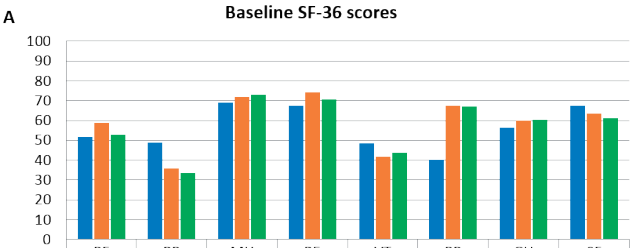
Patient satisfaction

The vast majority of patients were very satisfied with the esthetic appearance of the TPS at 3 months post-implant. This can be explained by the fact that TPS eliminates the need for the subcutaneous pocket.[5] In addition, most patients ranked their recovery, and the level of activity after implant as satisfied or very satisfied. Although the patient satisfaction questionnaire has not been validated, the results suggest that the VVIR pacing therapy using TPS might be effective and contributes to improved rehabilitation. However, without a randomized comparison to patient satisfaction after a conventional PM implant, it remains difficult to put these results in perspective.

Activity restrictions

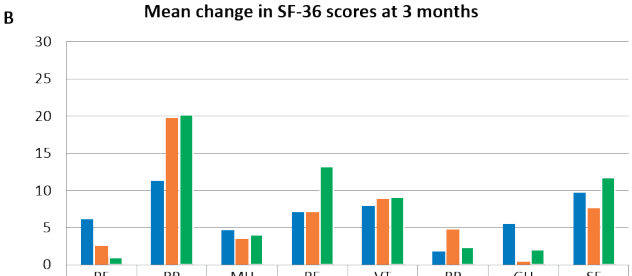
Implanting physicians should provide clear discharge mobilization instructions to minimize the risk for lead dislodgement following conventional PM therapy, considering early complications are mainly related to the leads or subcutaneous pocket.[1, 6-8, 16] Although this single-arm nonrandomized study is not a direct comparison to a control group with traditional pacing, a tendency to less activity restrictions has been reported by the implanting physicians. In current clinical practice, restrictions in patient activities are recommended for 4 to 6 weeks after conventional PM therapy. Extension and lifting above shoulder height of the arm adjacent to the PM are prohibited. In contrast, there are no post-TPS activity restrictions for shoulder and arm activities, since the TPS is not tethered to a lead. TPS activity restrictions, as defined by the implanting physicians, are primarily associated to the femoral puncture and 27Fr outer diameter sheath. Patients are mandated bed rest following TPS, to mitigate the risk for vascular complications at the groin puncture site. It is recommended that patients avoid heavy physical activity, such as heavy lifting, and sports for at least three days. A minority of implanting physicians (4%) considered TPS as more restrictive mostly as a consequence of prolonged immobilization post-procedure. It is conceivable that the large venous sheaths used for the deployment of the leadless PM potentially cause complications at the groin puncture site (e.g. hematomas, pseudoaneurysm and arteriovenous fistulas) and therefore might account for the prolonged bed rest.[5] However, Reynolds *et al.* demonstrated that only 0.7% of the patients developed a severe adverse event at the groin puncture site, but this number might not include incision site bleedings which are conservatively contained.[5]

A



	PF	RP	MH	RE	VT	BP	GH	SF
TPS	51,6	49,1	68,9	67,7	48,4	40,4	56,4	67,7
MOST	58,9	35,7	72,0	74,1	41,9	67,6	60,0	63,5
PASE	52,9	33,4	73,0	70,6	43,9	67,3	60,3	61,3

B



	PF	RP	MH	RE	VT	BP	GH	SF
TPS	6,2	11,3	4,7	7,1	7,9	1,8	5,5	9,7
MOST	2,6	19,8	3,5	7,1	8,9	4,8	0,4	7,6
PASE	1,0	20,2	4,0	13,2	9,1	2,4	2,0	11,7

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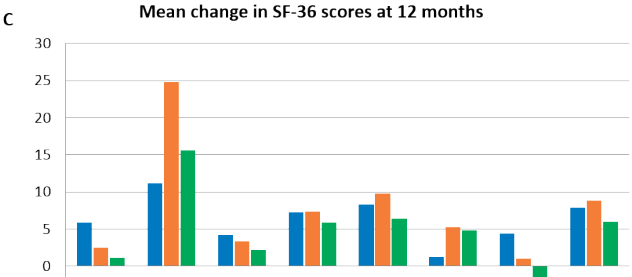

	PF	RP	MH	RE	VT	BP	GH	SF
TPS	5,9	11,2	4,2	7,3	8,3	1,3	4,4	7,9
MOST	2,5	24,8	3,4	7,4	9,8	5,3	1,0	8,8
PASE	1,1	15,6	2,2	5,9	6,4	4,8	-1,9	6,0

Figure 4. SF-36 scores of TPS compared to historic transvenous single-chamber pacemaker cohorts at baseline, 3 and 12 months

Panel A. The SF-36 scores for each domain at baseline are reported for all VVIR-pacemakers from three cohorts: Transcatheter Pacing Study (TPS), Mode Selection Study (MOST) [10] and the Pacemaker Selection in the Elderly (PASE) study [13].

Panel B. The change in SF-36 scores from baseline to 3 months post-implant for each domain are reported for all VVIR-pacemakers from three cohorts: TPS (present study), MOST and PASE.

Panel C. The change in SF-36 scores from baseline to 12 months post-implant for each domain are reported for all VVIR-pacemakers from three cohorts: TPS (present study), MOST and PASE. The 9-month SF-36 scores from the PASE study are presented here due to a lack of 12-month SF-36 scores. PF: physical functioning; RP: role physical; MH: mental health; RE: role emotional; VT: vitality; BP: bodily pain; GH: general health; SF: social functioning.

Limitations

The SF-36 is a well-validated and widely used tool to assess general HRQoL. However, it does not allow for a distinction whether the effect we observed was due to leadless pacing or pacing per se. Unfortunately, a disease specific or device specific questionnaire such as the Aquarel or the Florida Patient Acceptance Survey was not done.[21] Instead, non-validated questionnaires were used to assess patient satisfaction and activity restrictions following TPS therapy. Therefore, a comparison of the findings from the generic questionnaire to patients with similar disease and treatment cannot be performed. A substantial number of patients were excluded from the multivariate HRQoL analysis because only patients who completed the questionnaires at both baseline and 12-month post-implant were included. Further, although a large majority of patients was (very) satisfied with the esthetic appearance after TPS, it is unclear what the relevance of esthetics is in octogenarians. Several disease states have established clinically meaningful changes in SF-36 scores; however, we are not aware of such thresholds for norm-based scores in the pacemaker population. As such, our interpretation of the magnitude of change observed is limited to a statistical interpretation. Lastly, in 6 patients (0.8%) the Micra TPS implantation was unsuccessful and these were therefore excluded from this study. Despite the fact that this low implant failure rate would probably not substantially impact the overall findings, a complete HRQoL assessment, including unsuccessful attempts of the Micra TPS procedure, was not performed. More studies are required to evaluate the impact of TPS on HRQoL beyond 12 months post-implant.

Conclusion

In this large contemporary single-chamber PM cohort TPS resulted in post-implant HRQoL improvements at 3 and 12 months, along with high levels of patient satisfaction at 3 months. Further, TPS was associated with less activity restrictions compared to conventional PM systems. This makes TPS a viable treatment option in patients indicated for ventricular pacing therapy.

Funding
None.

Conflict of Interest
Fleur Tjong received consulting fees from Abbott and Boston Scientific. Joris de Groot received research support from Medtronic (institutional). Catherine Waweru and Shufeng Liu hold stock in Medtronic and are currently employed by this company. Philippe Ritter is consultant and principle investigator for the Micra Study. Dwight Reynolds is consultant/advisor for Medtronic. Niek Beurskens, Arthur Wilde and Reinoud Knops have no conflict of interest.

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PART

II

Challenges in Leadless Pacemaker Therapy

CHAPTER

5

The learning curve associated with the implantation of the Nanostim leadless pacemaker

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Background

Leadless pacemaker (LP) therapy was introduced to address the limitations of traditional transvenous implantable pacemakers (PM).[1] The Nanostim LP system (Abbott, Chicago, IL, USA) introduced in 2012, has revolutionized the state of pacing therapy. Reported short-term complication rates of LP therapy have been comparable to traditional PM therapy, but were different in nature.[2] However, when interpreting these results, the expected learning curve-associated with the implantation of a novel device using a unique set of tools must be considered. Procedure-related complications, such as cardiac injury, potentially relates to the novelty of the leadless technology and operator experience. As has been the case with other technologies, one can expect that the outcome and efficacy will improve with time and clinical experience.

Previous studies reported quantifiable outcome - and performance learning curves associated with the introduction of cardiac interventions, such as cardiac resynchronization therapy (CRT; [3]), subcutaneous defibrillators (S-ICD; [4]), and transcatheter aortic valve replacement (TAVR; [5,6]). To date, the learning effect of the Nanostim LP is unknown, yet is of paramount importance since it: 1) aids to the knowledge of the number of implants that have to be performed before reaching an acceptable level of competence, 2) may enhance and inform the appropriate training strategy, 3) is essential for the comparison with traditional PM therapy, and 4) is crucial to reach valid conclusions on its safety and efficacy.

We therefore sought to describe the learning curve for individual Nanostim LP operators in relation to serious adverse device effects (SADE) within 30 days. In addition, we aimed to evaluate the impact of operators' experience on procedural efficiency, according to procedure time and need for multiple repositioning attempts.

Methods

Study Cohort

This analysis included patients who were implanted with a right ventricular active-fixation Nanostim LP within two multicenter clinical trials conducted in Europe, US, Canada and Australia. Data were collected until March 16th 2017 for the Leadless Observational study (clinicaltrials.gov no. NCT02051972), and April 10th 2016 for the Leadless II IDE study (clinicaltrials.gov no. NCT02030418; [1]). Enrollment in the Leadless Observational study was temporarily paused from April 18, 2014 to June 2, 2014 because of the occurrence of 2 fatal cardiac perforations. Patients implanted prior and post-pause were included in the analysis. The implant technique of the Nanostim LP has been described previously.[7] All implanting physicians followed a validated implant training program organized by the device manufacturer. Both studies conform

to the ethical guidelines of the Declaration of Helsinki. Approval was obtained by each participating site's Institutional Review Board.

Endpoints

Endpoints in this analysis were: 1) SADE up to 30 days post-implant procedure, 2) procedure duration, 3) number of device repositioning attempts, and 4) pacing thresholds at implant. SADE were defined as any undesirable effect related to the device or implant procedure that resulted in: death, life threatening illness, prolongation of hospitalization, persistent or significant disability or incapacity. Procedure duration was defined as the time from venous access to removal of the introducer sheath. Device repositioning attempts was defined as the number of times the LP was implanted into the endocardium after the initial implant. All complications were reported by the participating sites and monitored by the study organization, and were adjudicated by the Clinical Events Committee of each study.

Statistical analysis

The combined data from the two studies were included in the analyses. The baseline characteristics were reported descriptively by experience quartiles using the mean ± standard deviation with the numbers of patients for continuous variables and numbers with percentages for dichotomous or categorical variables, unless otherwise indicated. P-values were computed for continuous variables using Kruskal-Wallis test with a non-normal distribution data, and for categorical variables using Chi-square test, or as appropriate. The number and rate of SADE up to 30 days post implant were presented, and the Kaplan Meier analyses and log rank test were used to assess event rates across groups.

The impact of individual implanter experience at the time of the implant on outcomes were analyzed. The total number of implants performed by each implanter were summarized and distributed equally in experience quartiles amongst all implanters. The ranking order of all implants per physician was determined by the implant date and time, and the patients were binned in quartiles based on this ranking number. The first quartile represents the initial experience of operators: the first two implants; the second quartile: the third to fifth implant; the third quartile: the sixth through tenth implant; and the fourth quartile represents operators with the most experience (i.e. more than 10 implants).

Univariable analyses were performed to investigate whether patient characteristics, pre/post-pause status, or study indication were associated with the endpoints analyzed. Logistic regression analysis was performed for the complications outcome and a general linear model was fit for the outcome procedure time. In the multivariable analyses, backward selection was used in model selection with a significance level for retention of 0.15. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina). P values <0.05 were deemed statistically significant.

Results

The pooled cohort consisted of 952 patients from the Leadless II IDE Study and 487 patients from the Leadless Observational Study, resulting in a total of 1439 patients who underwent a Nanostim LP implant performed by 171 implanters, at 60 centers in 10 countries. The median number of implants per operator was 5 (range 1 to 86). **Table 1** demonstrates the baseline characteristics per quartile categorized on gaining implant experience.

Table 1. Baseline characteristics per experience quartile

Characteristics	Quartiles				P-Value*
	Q1 (1-2)	Q2 (3-5)	Q3 (6-10)	Q4 (>10)	
Number of patients	317	325	311	486	n/a
Implanters	47	43	46	35	n/a
Demographics					
Age (years)	76.6 ± 11.3	75.6 ± 11.7	75.1 ± 12.9	74.9 ± 14.1	0.4145
Male	212 (66.9%)	203 (62.5%)	180 (57.9%)	305 (62.8%)	0.1422
BMI[a]	28.5 ± 6.1	28.5 ± 7.9	27.7 ± 5.9	27.7 ± 6.0	0.0811
Pacemaker indications					
Chronic AF[b] with 2nd or 3rd degree AV[c] block	195 (61.5%)	176 (54.2%)	170 (54.7%)	217 (44.7%)	<0.0001
Sinus rhythm with 2nd or 3rd degree AV block and a low level of physical activity or short expected lifespan	36 (11.4%)	48 (14.8%)	36 (11.6%)	91 (18.7%)	0.0091
Sinus bradycardia with infrequent pauses or unexplained syncope with EP[d] findings	87 (27.4%)	101 (31.1%)	105 (33.8%)	180 (37.0%)	0.0345
Medical History					
Congestive Heart Failure	53 (16.7%)	43 (13.2%)	37 (11.9%)	58 (11.9%)	0.2088
Hypertension	254 (80.1%)	249 (76.6%)	221(71.1%)	323 (66.5%)	<0.0001
Diabetes	83(26.2%)	77(23.7%)	64(20.6%)	116(23.9%)	0.4292
Peripheral Vascular Disease	34 (15.1%)	27 (11.4%)	21 (9.3%)	32 (12.2%)	0.2859
Coronary Artery Disease	114 (36.0%)	105 (32.3%)	96 (30.9%)	132 (27.2%)	0.0643
Myocardial Infarction	41 (12.9%)	40 (12.3%)	37 (11.9%)	57 (11.7%)	0.9621
Unstable Angina	10 (3.2%)	9 (2.8%)	7 (2.3%)	14 (2.9%)	0.9177
Prior PTCA[e] / Stents / Atherectomy	46 (14.5%)	39 (12.0%)	51 (16.4%)	62 (12.8%)	0.3567
Prior CABG[f]	51 (16.1%)	45(13.8%)	25 (8.0%)	49(10.1%)	0.0058
Ablation	30 (9.5%)	27 (8.3%)	41 (13.2%)	50 (10.3%)	0.2177
Medication					
Anticoagulants	201 (63.4%)	209 (64.3%)	186 (59.8%)	235 (48.4%)	<0.0001
Anti-platelets	131 (41.3%)	109 (33.5%)	117 (37.6%)	173 (35.6%)	0.1978

[a] p-values for continuous variables are computed using Kruskal-Wallis test, and for categorical variables using Chi-square test. A; BMI; body mass index, [b] AF; atrial fibrillation, [c] AV; atrioventricular, [d] EP electrophysiology, [e] PTCA; percutaneous transluminal coronary angioplasty, [f] CABG coronary artery bypass grafting

Impact on Serious Adverse Events

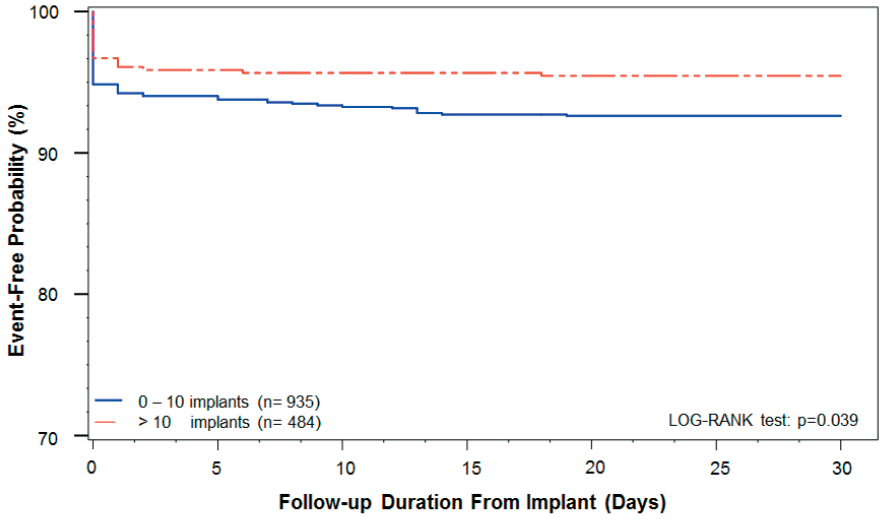
Of the 1439 included patients, 20 Pre-CE mark patients with missing implant - or SADE data were excluded, leaving a total of 1419 patients for this analysis. During a follow-up of 30 days, 91 (6.4%) patients experienced a total of 100 SADE, of whom 24 (1.7%) patients had a cardiac perforation, in 20 (1.5%) patients device dislodgement occurred, and 17 (1.2%) patients experienced vascular complications. Of the 24 cardiac perforations, 18 resulted in cardiac tamponade and 6 resulted in pericardial effusions without tamponade. In the 6 non-tamponade perforation cases, only 2 required intervention. There were 2 instances of cardiac perforations that lead to death of the patient. An overview of all SADE is illustrated in **Table 2**.

Table 2. Serious adverse events in the first 30 days.

Description	Number of Subjects with events	Number of Events	Percentage of subjects with events (n=1419)
Cardiac Perforation	**24**	**24**	**1.7**
Pericardial Effusion without Intervention	4	4	0.3
Pericardial Effusion with Intervention	2	2	0.1
Cardiac Tamponade	18	18	1.3
Vascular Complication	**17**	**17**	**1.2**
Access Site Bleeding Event	7	7	0.5
AV[a] Fistula	4	4	0.3
Vascular Access Site: Pseudoaneurysm	5	5	0.4
Perclose System Malfunction Requiring Surgical Intervention	1	1	0.1
Arrhythmia during device implantation	**12**	**12**	**0.8**
Asystole	2	2	0.1
Ventricular Tachycardia or Fibrillation	3	3	0.2
Conduction block	4	4	0.3
Other	3	3	0.2
Cardiopulmonary Arrest	**1**	**1**	**0.1**
Device Dislodgement	**20**	**20**	**1.4**
Device Malfunction	**7**	**7**	**0.5**
Threshold Elevation	5	5	0.4
Threshold Elevation Requiring Retrieval of LP[b]	1	1	0.1
Failure to Capture/Loss of Capture	1	1	0.1
Thrombo-embolic event	**6**	**6**	**0.4**
Ischemic Stroke	1	1	0.1
Probable Pulmonary Embolism	1	1	0.1
Thrombosis	1	1	0.1
Transient Ischemic Attack	3	3	0.2
Fever (unknown etiology)	**1**	**1**	**0.1**
Other	**10**	**12**	**0.7**
Total	**91**	**100**	**6.4**

A; AV; atrioventricular, b; LP leadless pacemaker

In the multivariable Logistic Regression analysis, age (Odds Ratio [OR] 1.02; 95% Confidence Interval [CI] 1.001 – 1.004; p=0.04), pre-pause indication (OR 2.72; 95%CI 1.15-6.41; p=0.02), myocardial infarction (OR 2.02; 95%CI 1.17-3.47; p=0.01), and non-right ventricular apex position of the device (OR 0.52; 95% CI 0.30-0.89; p=0.02) were associated with the endpoint measure of SADE. The 4th quartile (i.e. >10 implant attempts) was associated with a significant lower complication rate compared with the cumulative complication rate of the first three quartiles, 4.5% versus 7.4% respectively (p=0.038). The Kaplan-Meier curve showed that for implanting physicians who performed more than 10 procedures, 95.5% of patients remained free from SADE at 30 days post-implant, as illustrated in **Figure 1.**



Number at risk

0 – 10 implants	935	877	870	863	861	861	859
> 10 implants	484	464	462	462	461	461	461

Figure 1. Kaplan- Meier curve illustrating the estimation of remaining free from SADE at 30 days post-implant. The red line represents patients who underwent a Nanostim LP implantation by physicians who performed more than 10 procedures (group 1). The blue line are patients in whom the operator performed equal or less than 10 procedures (group 2). Thirty days event free rates following device implant in patients from group 1 was 95.5%, and patients from group 2 92.6% did not experience any type of SADE. (log rank p=0.039).

Patients in whom the operator performed equal to or less than 10 procedures, the event free rate of SADE was 92.6 % at 30 days following LP implant (log rank p=0.039). Cardiac perforation occurred in 2% of patients in quartile 1 through 3 compared to 1% in quartile 4 (p=0.197), as can be seen in the **Supplementary File 1**. In **Figure 2** the SADE rates per experience quartile are illustrated: quartile 1; 5.1%, quartile 2; 9.1%, quartile 3; 7.9% and quartile 4; 4.5% and quartile 1 to 3; 7.4% versus quartile 4; 4.5% (p=0.038).

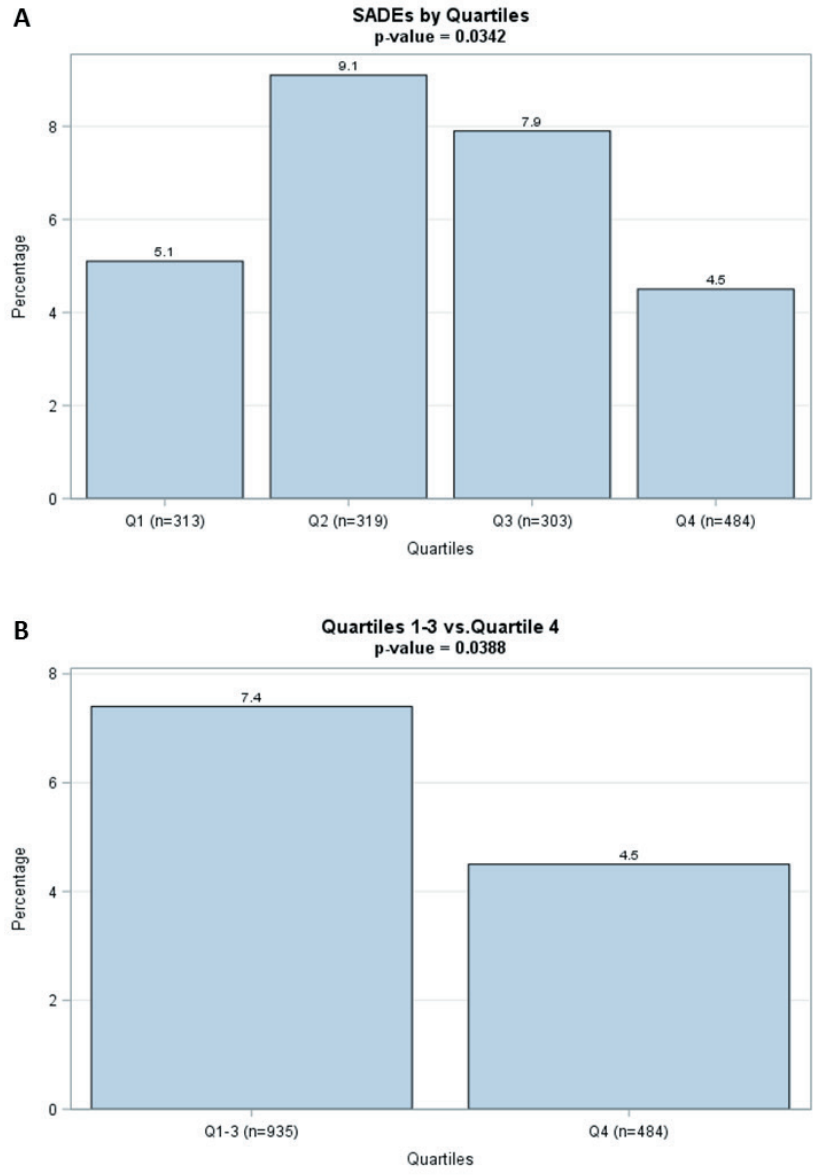


Figure 2. Panel A: Bar chart illustrating SADE in the first 30 days following Nanostim LP implantation per experience quartile. **Panel B:** Bar chart representing the SADE post Nanostim LP implant within 30 days. SADE dropped significantly after 10 implants per operator (Q4 versus Q1 to Q3).

Impact on Procedural Efficiency

In 51 patients the required data for procedural efficiency analysis was missing. These subjects were therefore excluded, resulting in a final cohort of 1368 patients. Total implant duration, which initially had a mean of 30.9 ± 19.1 minutes in the first quartile, decreased across the procedure quartiles to 21.6 ± 13.2 minutes ($p<0.001$, **Figure 3**).

Overall, successful implantation within a single deployment of the device was achieved in 78.7%, which can be seen in **Figure 4**. Requirement for multiple repositionings during the LP procedure was significantly less common among operators with the most experience (14.8%), compared to quartile 1 (26.8%; p<0.001), quartile 2 (26.6%; p<0.001) and quartile 3 (20.4%; p=0.03). Pacing thresholds at implant was not associated with operator experience. (**Supplementary File 2**)

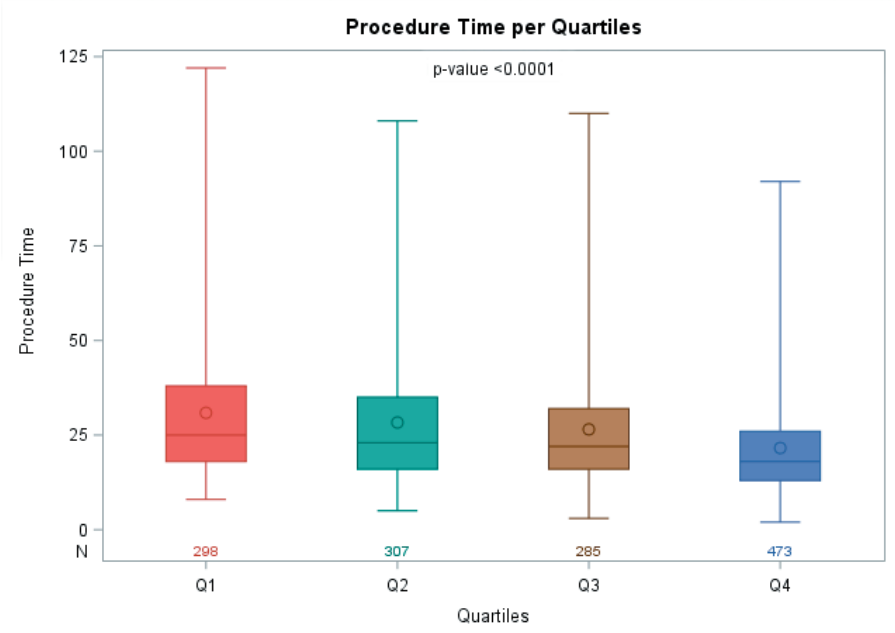


Figure 3. Boxplot showing Nanostim implantation time per experience quartile. The first quartile represents the initial experience of operators (1-2), the second quartile (3-5), the third quartile (6-10), and the fourth quartile represents operators with most experience (<10). The horizontal middle solid line of the boxplots corresponds to the median of the quartile. Total procedure duration significantly decreased across the procedure quartiles (p<0.0001). N number of patients; Q quartile.

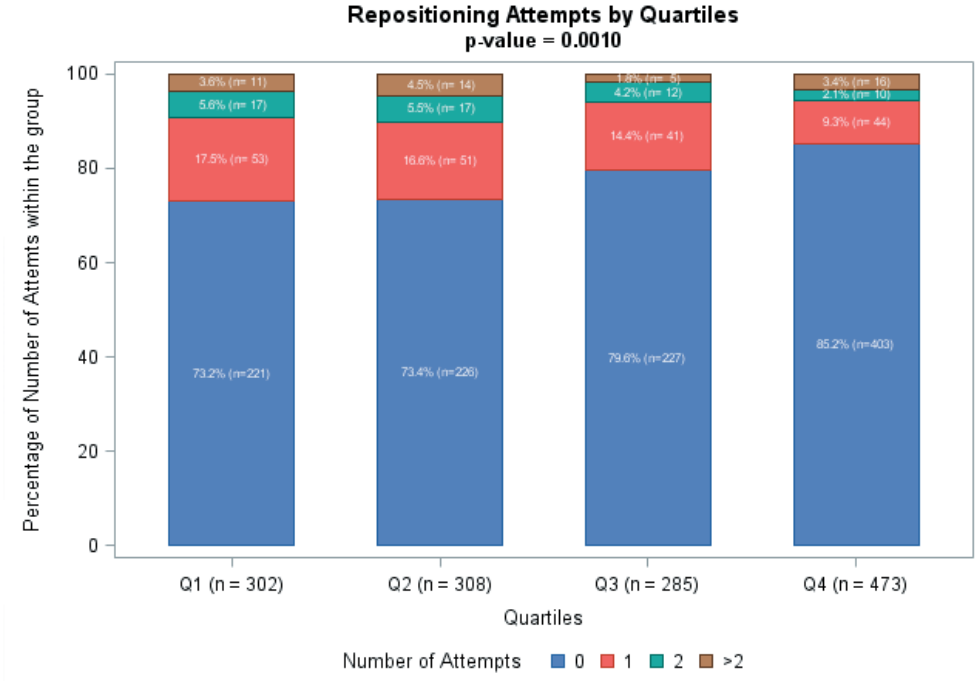


Figure 4. Bar chart illustrating the required number of device repositioning attempts per operators experience quartile. The purple area corresponds to no need for device repositioning, the red area represents 1 extra repositioning attempt, the green - and brown area, 2 and more than 2 additional repositioning attempts respectively. The need for multiple repositioning attempts during the Nanostim implant procedure reduced with increasing quartiles ($p<0.001$).

Discussion

There are two principle findings of the current study. First, complication rates of Nanostim LP therapy were low throughout early implant experience, but improved further after more than 10 implants per operator. Second, procedure efficiency significantly improved with gaining implant experience, based on a decrease in total procedure duration and reduction in the need for multiple repositionings.

Previous studies have shown that there is ample evidence for learning curves in newly introduced medical technologies, such as CRT, S-ICD, and TAVR.[3-6] These studies demonstrated consistent improvements in procedural parameters and metrics with increased experience until an asymptote was reached. Efficiency in performing CRT implants improved with increasing operator experience, with concomitant reduction of procedure and fluoroscopy time.[3] It took 10 implant attempts for the learning curve to reach its asymptote. For TAVR, 25 cases were needed before reaching an optimal level of competence, which translated in a decline of radiation and contrast exposure, together with a drop of complication rates.[6] Knops *et al.* demonstrated that complications

following S-ICD implantation, which initially occurred in 9.8% of cases significantly decreased to 5.4% over time, and stabilized at an asymptote of 12 implant attempts per operator.[4] In the current study, the data also shows a learning effect since operators in quartile 4 (most experience; more than 10 implants) had a significant lower complication rate compared with those who performed 1 through 10 procedures, 4.5% versus 7.4 % respectively. However, a different aspect of the learning curve was observed in our data. A notable low complication rate was seen during the initial experience of operators (i.e. 1 through 2 implants), followed by a significant rise (i.e. 3 through 10 implants) until a transition point was reached (i.e. more than 10 procedures) with concomitant lowest complication rates. This might partially be explained by the fact that all operators were tightly proctored during the initial implant attempts. In addition, one can imagine that the first and second implants of this novel technology were treated with the utmost care. A similar trend was observed for the occurrence of cardiac perforation during Nanostim LP implantation. SADE were associated with patient characteristics, such as older age and prior myocardial infarction, and procedural characteristics including right ventricular apex position of the device. In the initial phase of the LEADLESS Observational Trial, a right ventricular apical position was recommended; however, there were 2 instances of cardiac perforation that resulted in death which might partially be explained by the more easily penetrable RV apex compared to the current recommended more apicoseptal positioning of the device. Enrollment in the Leadless Observational study was temporary suspended because of these fatal cardiac perforations. Subsequently, all operators were obligated to participate in enhanced training, involving extensive animal lab and video training. This is likely responsible for our finding that pre-pause patients were more prone to the development of SADE. Moreover, it acknowledges the impact of proper training and gaining experience on the performance learning curve of the Nanostim LP. Notably, there was a lower prevalence of chronic atrial fibrillation, hypertension and anticoagulation use in in the more experienced quartiles. This was balanced by more implantations in patients with sinus rhythm and infrequent pauses or syncope in the experienced quartiles compared to more indications of chronic atrial fibrillation with bradycardia in the less experienced quartiles. Quartile 4 may therefore reflect a healthier patient population which may be less prone to complications, such as significant pericardial effusion. In the later stages of the trial, it was generally more accepted to implant a single-chamber LP device in patients who had potential indications aside from chronic atrial fibrillation with bradycardia. In contrast, there were a lower number of patients with prior coronary artery bypass grafting in the higher quartiles, which might be expected to have the opposite effect as prior coronary artery bypass grafting might be protective against effusion.

The Micra Transcatheter Pacing System (TPS; Medtronic, Minneapolis, MN, USA) is the other clinically available leadless PM for patients with a single-chamber pacing indication. [8] El-Chami and co-workers assessed the impact of operator experience on procedural

outcomes with regard to the Micra TPS. They reported an overall 30-day complication rate of 2.9%. No significant association between operator's implant number and complications on procedural quartile basis was observed. The complication rates among quartile one to three (i.e. 1 through 12 implants) was 2.9% versus 2.7 % in quartile 4 (i.e. more than 12 implants). There are differences between El-Chami *et al.* - and the present study that merits emphasis. The Micra TPS study population contained 726 subjects, which is substantially lower than our 1419 cases. In addition, different cut-offs per procedural quartiles were used. Also, there are differences in the leadless PM fixation mechanism - and steerable catheter design which may contribute to the contradictory results.[9,10] Moreover, the definition used for the primary safety outcome measure varies for the Nanostim LP and Micra TPS trials.[1,11] The standard definition (ISO 14555 3.36) of SADE was applied in the Nanostim LP trial, whereas the Micra TPS trial established a more narrow definition (major complications) as the criteria for the primary outcome measure. Cardiac perforation by the active helix of the Nanostim is an uncommon phenomenon but is considered an important and potentially fatal complication. The incidence of cardiac perforation with the Nanostim LP was comparable to the rate associated with the Micra TPS and traditional PM.[8, 12]

In line with El-Chami *et al.* results, procedure duration of the Nanostim LP implant significantly decreased by 30% over the experience quartiles.[8] Procedural experience may improve skill in the manipulation of the steerable catheter, which consequently results in a more efficient procedure over time. The Nanostim procedure duration observed in the fourth quartile is significantly shorter compared with the time needed to perform a conventional transvenous single-chamber PM implant (median 18 versus median 39 minutes, respectively; $p<0.001$). [13]

Our data showed that procedure experience impacts the number of device deployments required to obtain optimal pacing parameters. As expected, gaining experience enhances comfort with the steerable catheter which potentially abates the necessity for device repositioning. Of note, the need for multiple repositionings was low among all groups, and similar to El Chami *et al.* study, there was no significant association between procedure experience and the need for more than 2 repositionings.[8] As expected, pacing thresholds at implant were not associated with operator experience. This can be explained by the fact that pacing thresholds are affected by factors unrelated to operator experience such as the myocardial substrate, degree of injury at implant, and medications.

Limitations

This large study is associated with several limitations. First, the study includes multiple centers and implanters which makes it complicated to assess the learning curve per individual institution and implanter. Second, the learning curve data represents the

experience accumulated before and after the pause of the Nanostim LP, which may be a confounding aspect in the analysis. Third, other potential confounders such as unrecorded comorbidities may influence the learning curve. Last, all operators involved in this study had experience in the usage of catheter-based procedures and may therefore be less representative of physicians without such experience.

Conclusion

The incidence of SADE up to 30 days following Nanostim LP implant is significantly lower after 10 implants per operator. Performance efficacy improved over time, resulting in shorter procedure duration, and less frequent need for multiple repositionings. This indicates that the Nanostim LP implant procedure is subject to a learning effect. This knowledge has important implications with regards to physician education and training as well as when establishing competency requirements for implanting physicians.

Conflict of Interest

Dr. Tjong reports consulting fees from Boston Scientific Corporation, Inc. and St. Jude Medical/Abbott. Dr. Knops reports consulting fees, research grants and honoraria for Boston Scientific, consulting fees research grants with Medtronic and St. Jude Medical/Abbott. Dr. Neuzil reports consulting fees from St. Jude Medical/Abbott. Dr. Defaye reports consulting fees from St. Jude Medical/Abbott. Dr. Ip reports consulting fees from St. Jude Medical/Abbott. Dr. Guerrero reports consulting fees from St. Jude Medical/Abbott. Dr. Reddy reports consulting fees and research grants from St. Jude Medical/Abbott. Dr. Exner reports consulting fees from St. Jude Medical/Abbott. Dr. Sperzel reports consulting fees from St. Jude Medical/Abbott. The remaining authors have nothing to declare.

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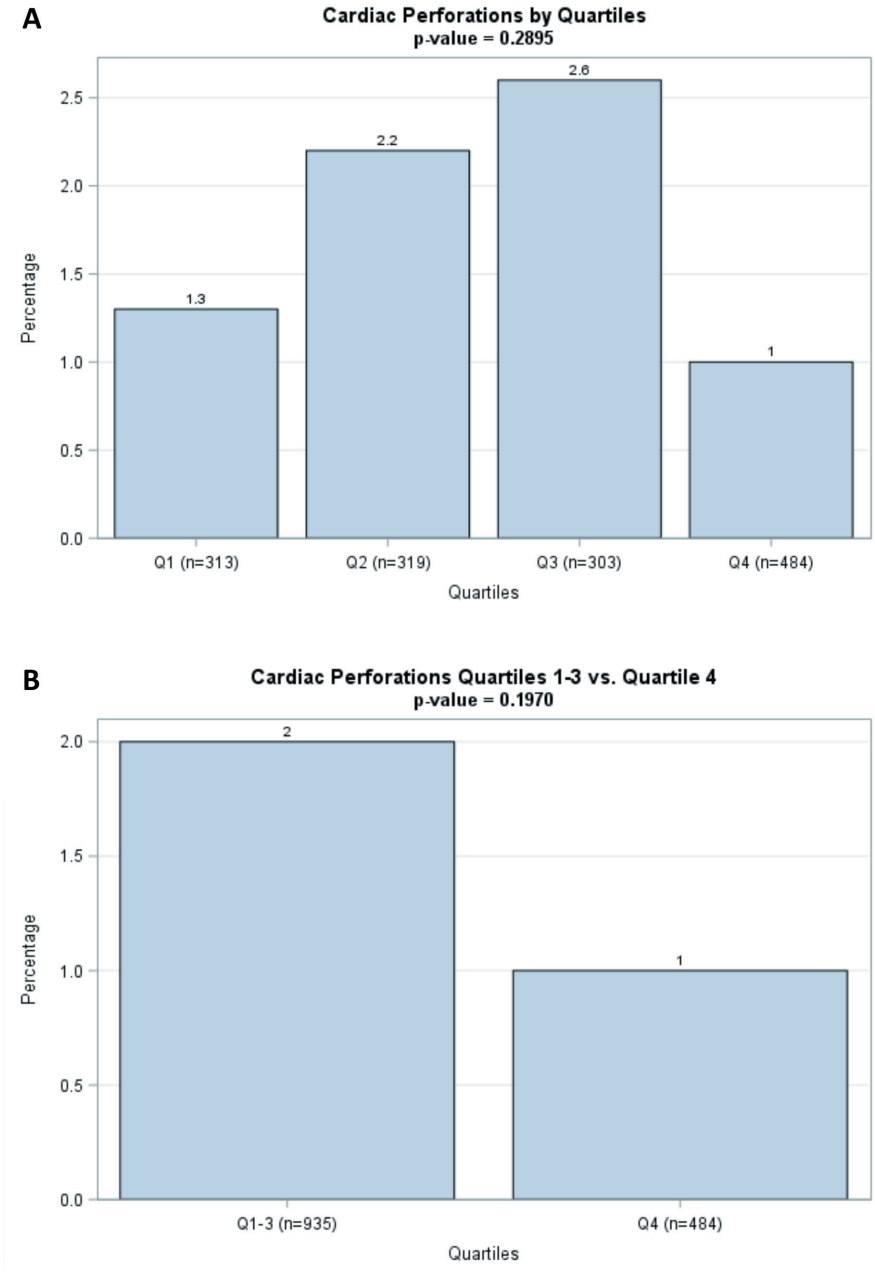
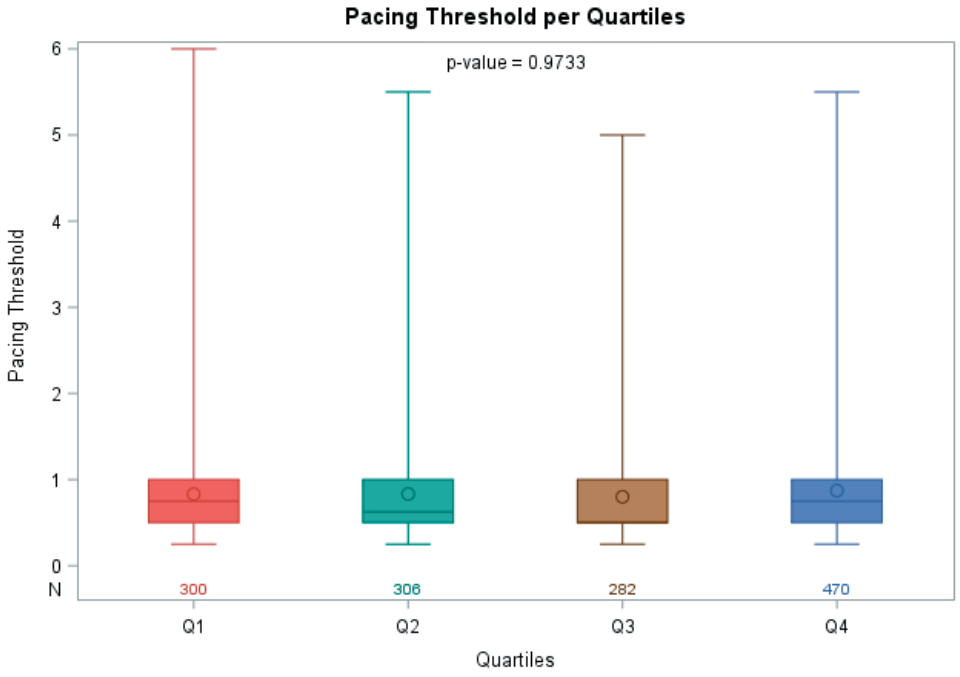


Supplementary File 1.

Panel A: Bar chart showing cardiac perforations as a consequence of the Nanostim LP implantation. A similar trend was observed between the occurrence of cardiac perforation compared with SADE per implantation experience quartile. **Panel B:** In 2% of patients cardiac perforation occurred in the first three quartiles, whereas in quartile 4; 1% of patients experienced cardiac perforation.



Supplementary File 2. Box plot displaying differences in pacing threshold at Nanostim implant per experience quartile. The horizontal middle solid line of the boxplots corresponds to the median of the quartile. No significant association observed between pacing thresholds at implant, and experience of the operator (p=0.97). N number of patients; Q quartile.

CHAPTER

6A

Successful replacement of the longest worldwide *in situ* Nanostim leadless cardiac pacemaker for a Micra Transcatheter Pacing System

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The potential inability to retrieve chronically implanted leadless pacemakers (LP) at end-of-life limits the application of this novel technology. Data on safe long-term LP retrieval is lacking, yet is of paramount importance. We present the case of an 80-year-old patient in whom a Nanostim LP was successfully implanted for chronic atrial fibrillation with symptomatic slow ventricular response in January 2013. Background history was notable for rheumatic aortic and mitral stenosis and status post mechanical aortic- and mitral valve replacement. At a regular follow-up visit 4 years and 9 months after LP implantation, the initial normal communication with the device was lost during impedance measurement, a known trigger for battery failure. The patient had 73% right ventricular pacing. Strategies to replace LPs reaching end of service remain an unsettled concern. Suggested strategies comprise of: placing an additional leadless device adjacent to the LP or retrieve the non-functioning LP and subsequently implanting a new device. We decided to extract the LP in order to limit the amount of non-functioning intracardiac hardware, mitigate the potential device-device interference and unknown long-term risks of multiple intracardiac devices. In addition, retrieval results in a more accessible right ventricle (RV) in case re-implantation of an additional device is indicated. The procedure was performed in the catheterization laboratory under fluoroscopic guidance and local anesthesia (Fig. 1).

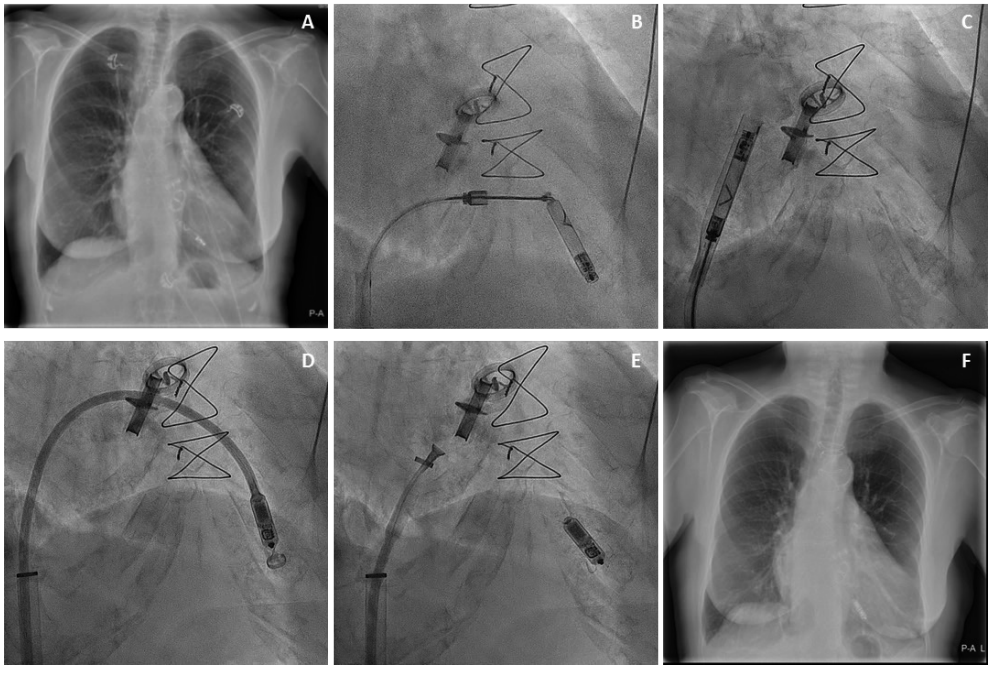

Figure 1. A: Chest radiography of the Nanostim, **B:** capture of the distal cap of the device by the snare at the end of the retrieval catheter, **C:** Nanostim removal from the RV, **D:** Micra insertion in the RV, **E:** Micra fixation in the right ventricular myocardium at a slightly different location (i.e. more septal) with the nitinol tines, **F:** Chest radiography of the Micra.

The retrieval catheter (Abbott) was percutaneously introduced via the femoral vein by using a 23F introducer sheath (Medtronic). The single-loop snare and the integrated protective sleeve at the end of the retrieval catheter were engaged towards the RV. The snare was engaged to capture the distal cap of the device. After docking the device, the helix was unscrewed from the endocardium. The protective sleeve was advanced over the LP and subsequently the device was removed. A Micra LP was inserted by the catheter delivery system (Medtronic) through the right femoral vein with the use of the same 23-French introducer (Medtronic). The Micra was fixated to the myocardium in the RV apex at a more septal position. The Micra implantation was completed without complications and with stable electrical parameters (i.e. RV sensing of >20 mV, impedance of 740 ohm and a pacing threshold of 0.38 Volts at 0.24 ms). Histopathological examination showed minimal adherent fibrous tissue at the proximal docking feature and helix of the Nanostim. We showed a safe and easy extraction of the longest worldwide *in situ* Nanostim. The feasibility of chronic uneventful LP retrievals, if confirmed by subsequent trials or follow-up studies, will demonstrate that there is an effective end-of-life device strategy, which makes LP a viable alternative to standard lead-based pacing. Considering the increasing incidence of patients in whom the Nanostim battery fails to meet their projected longevity, this information is highly relevant for all physicians implanting these devices.

CHAPTER

6B

End-of-life Management of Leadless Cardiac Pacemaker Therapy

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The clinically available leadless pacemakers (LP) for patients with a single-chamber pacing indication, have shown to be safe and effective. However, the optimal end-of-life (EOL) strategy of this novel technique is yet undefined. Suggested strategies comprise of: 1) placing an additional leadless device adjacent to the LP, or 2) retrieve the non-functioning LP and subsequently implanting a new device. Although the first studies demonstrate promising results, early experience on acute and mid-term retrieval feasibility and safety remains mixed. We suggest that the approach of LP retrieval is more appealing to limit the amount of non-functioning intracardiac hardware. In addition, potential risks for device-device interference, and unknown long-term complications associated with multiple intracardiac devices are prevented. The potential inability to retrieve chronically implanted LPs limits the application of this novel technology. Therefore, long-term prospective analysis is required to define the most optimal EOL strategy.

Clinical perspective in bullet points

1. Optimal End-of Life management of Leadless Pacemaker Therapy is subject to debate.
2. There are two strategies to address replacement strategy of leadless pacemakers: 1) placing an additional leadless device adjacent to the non-functioning leadless pacemaker, or 2) retrieve the non-functioning leadless pacemaker and subsequently implanting a new device.
3. There are clinical scenario's that have valid arguments for both aforementioned End-of-Life strategies.
4. We suggest that the approach of LP retrieval is more appealing to limit the amount of non-functioning intracardiac hardware, mitigate risk for device interference, and limit unknown long-term complications associated with multiple chronic implanted leadless pacemakers.

Introduction

Since its introduction in 2012, leadless pacemaker (LP) therapy has developed as a therapeutic alternative to conventional transvenous pacemaker (PM) therapy to circumvent lead- and pocket-related complications.[1-4] To date, two LPs are available for patients with a single-chamber pacing (VVI) indication: the Nanostim Leadless Cardiac Pacemaker (LCP; Abbott, Chicago, IL, USA) and the Micra Transcatheter Pacing System (TPS; Medtronic, Minneapolis, MN, USA).

The LPs have shown to meet the pre-specified safety and performance criteria in two large prospective multicenter single-arm studies.[3,4] The LPs demonstrated similar pacing performance and safety results, and exhibit high implantation success rates.[5] Reynolds *et al.* performed a post hoc analysis of patients who received Micra TPS implantation compared with the patients who underwent transvenous PM therapy in a historical control cohort. Micra TPS had fewer major complications compared to the patients in the historical control cohort at six months follow-up, 4.0% versus 7.4% respectively. [3] Reddy *et al.* demonstrated that long-term complication rates are expected to decrease by 71% following Nanostim LCP implantation compared to conventional transvenous PM therapy.[6]

Despite these promising results, there is an important challenge to consider: the end-of-life (EOL) management of LP therapy. The optimal approach at the end of service of conventional transvenous PM therapy has been studied in great detail.[7,8] The subcutaneous generator is readily accessible for replacement, leaving the leads in place.[7] PM lead extraction can be a high-risk procedure and is associated with serious complications including cardiac perforation and death.[8] Up to three leads can be placed intracardially, without hemodynamic compromise.[7] Optimal EOL strategy of LP therapy is subject to debate. The estimated battery longevity of the LP ranges between 4.7 and 15 years, depending on pacing parameters.[2,3,9] Therefore, selected patients might require multiple devices over their lifespan. Once the EOL of the LP approaches, there are two options for implanting physicians to address this problem. LPs were designed so that they can be programmed in a non-functional mode. The LP can be abandoned and an additional device may be implanted adjacent to the non-functional LP. Important concerns have been raised regarding the aforementioned option. Multiple devices in the heart may compromise cardiac function, or be a source of interference. The second replacement strategy is to extract the LP and subsequently implant a new device. However, extraction may not be feasible due to encapsulation of the device, and this will probably be more prevalent with more chronic use of LP therapy. Of note, there are situations where extraction of the LP may be necessary, such as in infection, or dislocation. Recently, a battery advisory was distributed by Abbott stating that 7 of 1423 (0.5%) patients had a

battery malfunction that occurred more than two years post Nanostim LCP implantation. This battery dysfunction has not been shown to affect Micra TPS.

With the battery advisory and the more chronic use of LPs, recommendations for EOL management becomes increasingly important. Therefore, an up-to-date review of available evidence on retrieval of LPs is highly clinically relevant. In this review we describe the safety, feasibility and histopathological examination of LP retrieval.

Leadless pacemaker and retrieval systems

Both LPs are cylindrical intracardiac devices, however there are differences in design that merit emphasis. The Nanostim LCP is 42mm long and 6mm in diameter, whereas the Micra TPS measures 26mm in length and 6.7mm in diameter. The characteristics of the devices are showed in Figure 1. Implantation of the devices is performed in the catheterization laboratory, under fluoroscopy. An introducer sheath (21F outer diameter [OD] for the Nanostim and 27F OD for the Micra TPS) is percutaneously placed in the femoral vein to deliver the device through the vena cava inferior towards the right ventricle (RV) using a steerable catheter. The Nanostim LCP uses an active helix to fixate the LP into the cardiac tissue of the RV. The Micra TPS is anchored into the right ventricular myocardium using an active fixation mechanism that is composed of four Nitinol tines.

Leadless Pacemakers	**Nanostim LCP**	**Micra TPS**
		
Dimensions, mm	42.0 x 5.99	25.9 x 6.7
Volume, cc	1	0.8
Weight, g	2	2
Sheath Size, Fr	21 OD/ 18 ID	27 OD/ 23 ID
Battery Longevity, yrs	8.5 – 9.8	4.7 – 9.6
Fixation Mechanism	Helix	4 Ninotol Tines

Figure 1. The characteristics of the clinically available leadless pacemakers. Left: the Nanostim Leadless Cardiac Pacemaker (Abbott, Chicago, IL, USA). Right: the Micra Transcatheter Pacing System (Medtronic, Minneapolis, MN, USA).

cc cubic centimeter; ID inner diameter; Fr French; g gram; LCP leadless cardiac pacemaker; mm millimeter; OD outer diameter; TPS transcatheter pacing system; yrs years

The Nanostim LCP and the Micra TPS have different retrieval tools available. The manufacturers of the Nanostim LCP developed a dedicated steerable retrieval catheter to allow retrieval of the device. The retrieval catheter is introduced via the femoral vein through a 18F sheath. The snare (single-loop or triple-loop) and the integrated protective sleeve at the end of the retrieval catheter are engaged under fluoroscopic guidance from the vena cava inferior towards the right atrium. The protective sleeve is retracted when positioned near the Nanostim LCP, and the single- or triple-loop snare is engaged to capture the distal cap of the LP in the RV. The snare is closed to grab the proximal docking feature of the device. After docking the Nanostim LCP, the helix can be unscrewed with two full rotations from the endocardium by turning it counterclockwise. The protective sleeve is advanced over the total LCP, and it can be removed from the body. The Micra TPS does not have a dedicated retrieval system. It was designed with a retrieval feature at the proximal end of the LP to accommodate an off-the-shelf snare which can hold the device for removal from the myocardium. A conventional gooseneck snare alone or inserted through the delivery catheter can be used for the retrieval. The advantage of the latter option is that counter traction can be applied to the myocardium with the cup of the implant catheter. In Figure 2 the retrieval of the LP systems are illustrated.

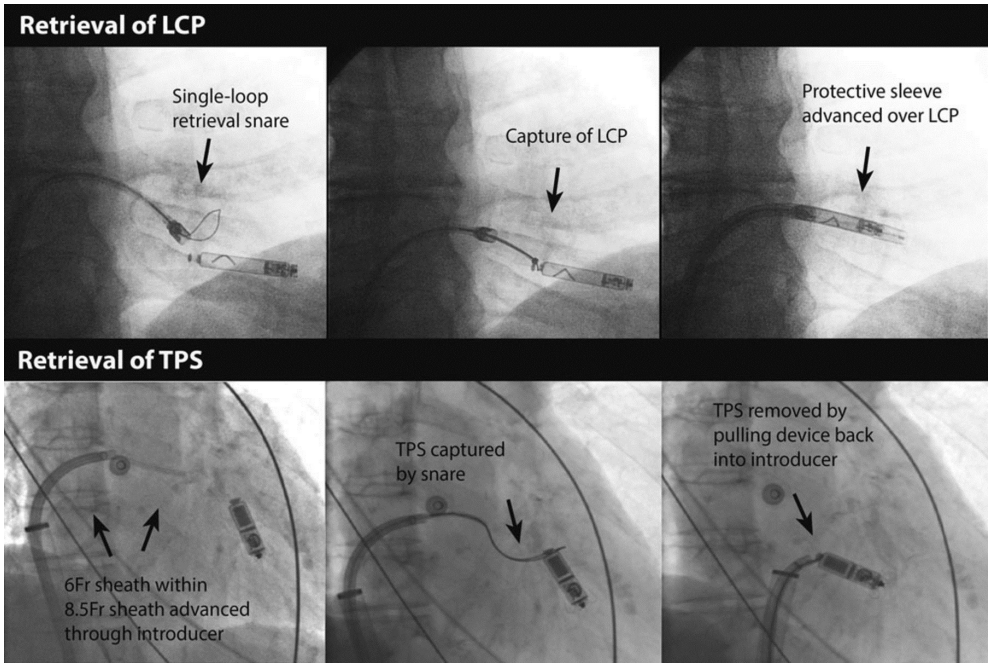

Figure 2. The retrieval of the leadless pacemakers. Nanostim LCP (upper) and the Micra TPS (bottom). The retrieval catheter is introduced via the femoral vein towards the right atrium. The snare at the end of the retrieval catheter is engaged under fluoroscopic to capture the retrieval features of the LPs. After docking the Nanostim LCP, the helix can be unscrewed with two full rotations from the endocardium by turning it counterclockwise. For the Micra TPS, the snare grabs the waist of the retrieval feature and the device is pulled out from the myocardium while exerting controlled counter pressure using the sheaths.

Fr French; LCP Leadless Cardiac Pacemaker; TPS Transcatheter

Pre-clinical data on retrieval and multiple implanted leadless pacemakers

Nanostim Leadless Pacemaker

Early animal experience on retrieval of the Nanostim LCP has shown positive results. Koruth *et al.* evaluated the mid-term and long-term feasibility and safety of percutaneous, catheter-based retrieval of the Nanostim LCP in an ovine study.[10] To evaluate mid-term retrieval capability, ten sheep underwent retrieval at a mean of 160 days, and in eight additional sheep the Nanostim LCP was extracted at a mean of 2.3 years. All mid-term and long-term retrieval attempts showed a 100% success rate. Echocardiographic pre- and post-implant evaluation showed no signs of pericardial effusion. For the mid-term group, the catheter time needed to retrieve the LP was 2:35 minutes, whereas for the long-term group this was 3:04 minutes. The relative short retrieval times underline the ease of the retrieval attempts. It is important to note that histological characteristics of ovine myocardium and its reaction to the device may be different compared to the human heart.

Micra Transcatheter Pacing System

Early pre-clinical animal experience demonstrated successful retrievals of three out of four ovines up to 28 months after Micra TPS implantation.[11] The unsuccessful attempt was due to fully encapsulation of the device. It has been suggested that a new LP can be placed adjacent to the abandoned non-functional LP. However, two important issues arise: 1) the maximum number of LPs the RV can accommodate anatomically and 2) the effect of multiple intracardiac devices on RV function. Therefore, Omdahl *et al.* evaluated the number of Micra TPS that could be placed in cadaver human hearts.[12] Seven hearts were successfully implanted with three Micra TPS in traditional pacing locations using standard implantation procedures. They concluded that the RV was able to accommodate three Micra TPS without physical interaction, even in a small RV of 35cc. However, mechanical or electric interactions between intracardiac Micra TPS may be different in contracting human hearts. To assess the effect of multiple LPs on the RV cardiac function, Chen *et al.* sequentially implanted two Micra TPS within one month in fourteen pigs.[13] Of all pigs who underwent implantation procedures, five animals died prior to the end of the 6-month follow-up. Echocardiography was performed at baseline, at second implantation, and at the end of the 6-month follow-up. Chen and co-workers showed no significant changes in cardiac proportions based on echocardiography and no observation of injury to the tricuspid valve.

Clinical data on leadless pacemaker retrieval

Nanostim Leadless Pacemaker

Jung *et al.* described a case of the successful retrieval of a Nanostim LCP at 506 days post-implant.[14] The reason for extraction was because the patient had an indication for

cardiac resynchronization therapy. Reddy *et al.* performed a multicenter study, wherein they evaluated feasibility and safety of retrieval before and after six months post Nanostim LCP implantation in 16 patients.[15] The mean time from LCP implantation to retrieval attempt was 240 days. The indications for retrieval were elevated pacing thresholds (n=8), deterioration of heart failure (n=5), pacing failure (n=1), defibrillator implantation (n=1) and elective explantation (n=1). The success-rate was 94% (15 of 16 patients). For the unsuccessful retrieval attempt, the device had been implanted for 103 days. The docking feature could not be reached due to its location near the tricuspid valve. A new Nanostim LCP was implanted adjacent to the initial LCP, and no procedure-related adverse events were reported. In Lakkireddy *et al.* study, the worldwide experience on battery failure and Nanostim retrieval was evaluated.[16] An attempt for retrieval was performed in 73 patients following Nanostim LCP implantation. The time that the Nanostim LCP was implanted in the heart ranged from 0.2-4.0 years. In 66 of these cases the retrieval attempts were successful (i.e. 90.4%). Another 115 patients received an additional LP or conventional transvenous PM adjacent to the abandoned Nanostim LCP due to the advisory. No adverse hemodynamic, mechanical or electrical interactions were reported. In two cases a serious adverse occurred that was related to the Nanostim LCP retrieval. In one case an atriovenous fistula developed and in one case the docking button detached and migrated into the pulmonary artery.

Micra Transcatheter Pacing System

Tjong and Reddy reported that thirteen patients who underwent Micra TPS implantation required a system revision.[5] The indications for revision were due to pacemaker syndrome, elevated thresholds, upgrade to biventricular pacing, and device infection. In 8 of 10 patients the attempt for retrieval was successful. For the unsuccessful attempts, the Micra TPS were 229 and 259 days in situ.[17] One of these Micra devices was snared but was unable to be removed due to fluoroscopy malfunction. In the three remaining patients who required system revision, retrieval was not attempted, and the device was abandoned. Karim *et al.* reported the first successful extraction of a Micra TPS in a patient three weeks after initial device implantation.[18] The Micra TPS had elevated capture thresholds. The automated capture management algorithm consequently increased the pacing output. Since the expected battery longevity would decline substantially, the physicians decided to retrieve the Micra TPS and subsequently implant a new LP. In contrary, one case was presented at the 37th Heart Rhythm Society Scientific Sessions (San Francisco, USA) which demonstrated an unsuccessful retrieval of the device implanted after 228 days.[19] Koay *et al.* was the first investigator who described the extraction of an infected Micra TPS.[20] The patient developed symptoms of infection one month after Micra TPS implantation. Transesophageal echocardiography demonstrated a vegetation attached to the proximal part of the device. Device interrogation demonstrated elevated capture threshold and increased pacing output. Therefore, it was decided to extract the Micra TPS and this

proceeded uneventful. Gerdes *et al.* described a case of Micra TPS retrieval after tether removal, while no standard correctly dimensioned snare was available.[21] A steerable sheath (Agilis, St Jude Medical) was engaged into the introducer, however incongruent proportions led to blood leakage from the introducer. After manually solving this problem, a standard 6F 20 mm snare kit (Amplatz Goose Neck) was inserted to withdraw the Micra TPS. Subsequently, a new Micra TPS was successfully implanted. An overview on retrieval data of LP therapy is displayed in Table 1.

Table 1.

Study type	Leadless Pacemaker	Year of publication	First author	Number	Time LP *in situ* (mean)	Extraction success rate	Reason unsuccessful extraction
Pre-clinical	Nanostim	2014	Koruth	10 8	160 days 2.3 years	100% 100%	N/A N/A
	Micra TPS	2014	Bonner	4	28 months	75% (3)	Complete encapsulation of device
Clinical	Nanostim	2016	Jung	1	506 days	100%	N/A
	Nanostim	2016	Reddy	5 10	<6 weeks >6 week	100% 91% (9)	 The docking feature could not be reached
	Nanostim	2017	Lakireddy	73	1.7 years	90.4% (66)	The docking button could not be reached in six cases. In one case, the docking button detached.
	Micra TPS	2017	Tjong and Reddy	10	229 and 259 days *	80% (8)	Unable to be removed due to fluoroscopy malfunction
	Micra TPS	2016	Karim	1	3 weeks	100%	N/A
	Micra TPS	2016**	Giocondo	1	228 days	0%	Unknown
	Micra TPS	2016	Koay	1	1 month	100%	N/A
	Micra TPS	2016	Gerdes	1	Intra-procedural	100%	N/A

LP leadless pacemaker; N/A not applicable; TPS transcatheter pacing system
** In the unsuccessful attempt cases. Reference: Micra Transcatheter Pacing System. FDA Panel pack for Circulatory Systems Devices Panel 2016.*
***Heart Rhythm Society Poster Session 2016. Unsuccessful extraction of a Medtronic Micra Leadless Pacemaker*

Histopathological examination

Occurrence of encapsulation and histopathological evaluation of the LP is highly relevant since it may influence the LP retrieval management. Fibrous tissue formation might complicate the recapture of the device. Therefore, multiple (non-)clinical studies and case reports have been published addressing this topic.

Nanostim Leadless Pacemaker

Koruth *et al.* performed pathological examination of the Nanostim LCP in an ovine study in which devices had been implanted for a mean of 2.3 years.[10] They showed that there was no visible tissue on the body of the LCP. There was little fibrous tissue located at the proximal docking feature, and distal helix. Some (sub)endocardial hemorrhage was observed at the implant site in the RV apex. In Reddy's *et al.* study, sixteen patients with a Nanostim LCP underwent a retrieval attempt at mean of 240 days.[15] Although no pathological evaluation was performed, visual inspection showed that in ten out of sixteen (63%) patients fibrous tissue was present on the docking knob or helix, and in one there was near-complete device encapsulation. Tjong *et al*. described a patient's postmortem histological examination at nineteen months after Nanostim LCP implant. [22] The evaluation revealed partial (i.e. approximately 60%), ongoing myofibrocellular encapsulation around the Nanostim LCP.

Micra Transcatheter Pacing System

In a swine study performed by Chen *et al.*, nine animals reached the endpoint with a mean follow up of 215 days.[13] Necropsy and histopathological examination showed little fibrous tissue around the extracted Micra TPS, and there were no observations of tricuspid valve injury. Complete encapsulation of the Micra TPS has been observed during autopsy of a patient one year after Micra TPS implantation.[23] This Micra TPS was adherent to the adjacent papillary muscle and immunohistochemistry revealed signs of chronic inflammation around the Micra TPS. In a pre-clinical study, one of four Micra TPS was not retrievable at 28 months following implantation.[11] Necropsy analysis of the unsuccessful retrieval attempt demonstrated the device was fully encapsulated. In Koay's *et al.* case report, the infected Micra TPS which was successfully extracted was covered with a thin layer of fibrous tissue firmly attached to all the fixation tines.[20] The histopathological examination demonstrated fibrous tissue with infiltration of neutrophils and histiocytes, confirming the existence of inflammation.

Recommendations and perspectives

Strategies to replace LPs reaching end of service remain an unsettled concern. One option is to abandon a non-functional LP and place an additional device in the RV. The volume of the LPs (0.8–1.0 cc) occupies less than 2% of the normal RV volume[24], consequently causing negligible hemodynamic compromise. In Lakkireddy *et al.* study no device-device related adverse events were reported in 115 patients in whom a new device was implanted adjacent to the abandoned Nanostim LCP.[16] Electrical interaction between the functioning and non-functioning device is unlikely, however there is currently no long-term evidence available to confirm this assumption. In selected cases, one can assume that attempting extraction of a fully encapsulated LP may have higher risk than

leaving the device in place. Progressive encapsulation over time might make retrieval even impossible without open-heart surgery. Although the aforementioned clinical scenario's show that there are valid arguments for this EOL strategy, we suggest that the approach of extracting the LP is more appealing in order to limit the amount of non-functioning intracardiac hardware. By extracting the non-functioning LP, the potential risk for device-device interference is mitigated, as well as unknown long-term risks associated with multiple devices in situ. In addition, the option of retrieval may result in a more accessible RV in case re-implantation of an additional device is indicated.

Several strategies should be implemented to prevent early battery depletion. It is recommended to avoid relatively high pacing thresholds since it inversely effects battery longevity of the LP. Economic programming of the LP may positively influence battery longevity, especially in non-pacemaker dependent patients. In these patients, pacemaker outputs can be programmed close to the pacing threshold. Therefore, Micra TPS has an automatic capture management to ensure pacing outputs remain at safe levels while adapting outputs to maximize battery longevity.

It is evident that incorporating a long-life self-rechargeable battery, or even no battery, would provide a major improvement in cardiac pacing therapy. A permanent pacemaker system capable of self-recharging would circumvent disadvantages related to PM replacement and eliminate its related risks. It was shown in a pre-clinical study that lead- and batteryless pacing was feasible using its own heart motion.[25] In another pre-clinical study, a batteryless PM was developed which was powered by a solar module that converted transcutaneous light into electrical energy.[26] This PM was able to provide pacing therapy continuously at a rate of 125 beats per minute 1½ months in the dark.

Retrieval of the LP remains an essential consideration for patients who are potentially eligible for leadless VVI pacing therapy. The potential inability to retrieve chronically implanted devices may limit the application of this novel technology in selected cases. Although first studies demonstrated promising results, early experience on retrieval feasibility and safety of LP therapy is mixed. Therefore, long-term prospective analysis is required to define the most optimal EOL strategy concerning LP therapy.

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CHAPTER

7

The impact of leadless pacemaker therapy on cardiac and atrioventricular valve function through 12 months' follow-up

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Background Endocardial pacemaker leads and right ventricular (RV) pacing are well-known causes of tricuspid valve (TV), mitral valve (MV) and cardiac dysfunction. Lead-related adverse consequences can potentially be mitigated by LP therapy by eliminating the presence of a transvalvular lead. This study assessed the impact of leadless pacemaker (LP) placement on cardiac and valvular structure and function.

Methods Echocardiographic studies before and 12 ± 1 months after LP implantation were performed between January 2013 and May 2018 at our center.

Results A total of 53 patients were included, of whom 28 were implanted with a Nanostim and 25 with a Micra LP device. TV regurgitation (TR) was graded as being more severe in 23 (43%) of patients at 12 ± 1 months compared to baseline ($p<0.001$). A more RV septal position of the LP (odds ratio 5.20, 95% confidence interval 1.22-22.2, $p= 0.03$) was associated with increasing TV incompetence. An increase in MV regurgitation (MR) was observed in 17 (38%) of patients ($p=0.006$). LP implantation resulted in a reduction of RV function, according to a lower tricuspid annular plane systolic excursion (18.6 ± 6.81 versus 16.2 ± 6.52 mm, $p=0.003$) and RV tricuspid lateral annular systolic velocity (11.8 ± 3.04 versus 10.9 ± 2.49 cm/s, $p=0.02$), and a higher RV Tei index (0.40 ± 0.10 versus 0.50 ± 0.16, $p=0.04$). LP implantation was further associated with a reduction of left ventricular (LV) ejection fraction (53.5 ± 8.55 versus 50.2 ± 8.55%, $p=0.03$) and elevated LV Tei index (0.48 ± 0.12 versus 0.69 ± 0.27, $p=0.003$).

Conclusions LP therapy is unexpectedly associated with an increase in TV dysfunction through 12 months' follow-up, most likely due to the mechanical impact of the intracardiac device on the TV or its subvalvular apparatus. Furthermore, LP therapy seems to adversely impact MV and biventricular function.

Keywords: Leadless Pacemaker Therapy, Micra Transcatheter Pacing System, Nanostim Leadless Cardiac Pacemaker, Atrioventricular valve and cardiac function, Echocardiography

Abstract

Introduction

Lead-based conventional pacemaker (PM) therapy is associated with development or intensification of tricuspid valve (TV) regurgitation (TR) in 25 to 50% of cases.[1,2] The clinical presentation of TR varies widely, yet can result in incremental morbidity and mortality. Intensification of TR is likely a consequence of damage to the TV leaflets or subvalvular apparatus during lead implantation on the one hand; and the long-term mechanical impact of the transvalvular lead on the other hand.[3,4] Furthermore, studies implicate that right ventricular (RV) pacing-induced ventricular dyssynchrony is associated with an increase in TV incompetence, in addition to mitral valve (MV), and cardiac dysfunction in PM recipients.[3, 5-10]

Leadless pacemaker (LP) therapy was developed to address the limitations of standard lead-based pacing.[11,12] Lead-related TV dysfunction can potentially be ameliorated by this novel approach, since the continuous mechanical impact of the lead on the TV is eliminated. Similar to conventional RV pacing systems, LPs are often placed in the RV apex because of its relative easy accessibility. LP therapy may therefore induce a similar abnormal electrical and mechanical activation pattern of the ventricles.

Studies evaluating mid and long-term cardiac morphology and function following LP therapy are lacking. These studies are of paramount importance since they will provide interesting insights into the mechanisms of TR, MV regurgitation (MR), and ventricular dysfunction and to delineate if these mechanisms are mechanically caused by the transvalvular leads or by electrical dyssynchrony from RV pacing.

Therefore, we sought to establish the effect of LP therapy (i.e. Abbott, Nanostim and Medtroninc, Micra) on heart structure and function at 12 months post-implant.

Methods

Patients underwent an echocardiographic study before and 12 ± 1 months after Nanostim or Micra LP implantation between January 2013 and May 2018 at the Amsterdam UMC, location Academic Medical Center (AMC). We used the data of a prospectively acquired population that comprised consecutive patients who underwent LP implantation at our center. A specific LP echocardiographic protocol was composed. The echocardiograms were performed in the setting of regular clinical care and were retrospectively assessed. Patients were excluded if echocardiographic image quality was insufficient for the evaluation of cardiac and valvular morphology. In addition, specific echocardiographic studies were excluded if its assessment was not feasible or unreliable (e.g. Tei indices in patients with atrial fibrillation and deviating PR duration). In these patients, the remaining

echocardiographic parameters were included in the analysis. Implantation of the device was performed in the catheterization laboratory by two electrophysiologist, according to current recommendations.[13]

The study conforms to the ethical guidelines of the Declaration of Helsinki. Ethical approval was obtained by the Medical Ethics Committee at the Academic Medical Center–University of Amsterdam, The Netherlands. All patients provided written informed consent.

Echocardiographic protocol and assessment

At our center, a Vivid 7 or 9 machine (GE Vingmed Ultrasound AS, Horten, Norway) was used for echocardiographic image acquisition. Echocardiographic recordings were performed using a 1.6-MHz to 3.2-MHz transducer (System 7 or 9; GE Healthcare, Milwaukee, WI). These recordings were digitized and subsequently assessed by an experienced echocardiographer. All echocardiographic images and indices were obtained according to current guidelines.[14] The mean value of three repetitive measurements was used for patients in sinus rhythm and five measurements in those with atrial fibrillation.

In patients with no atrial fibrillation, for determining the degree of MR, quantitative data from color Doppler involving the color-flow jet area in the left atrium and pulmonary vein flow were used. The TR was assessed according to Lancelotti's European Association of Cardiovascular Imaging Echo Guidelines. The degree of TR was based on the color-flow jet area in the right atrium by using the apical four chamber view in addition to continuous wave Doppler, pulsed wave Doppler, peak tricuspid systolic inflow, vena contracta diameter, and liver vein flow. TR and MR severity were categorized into 5 groups (i.e. 0 to 4; 0= none, 1 = mild, 2 = mild to moderate, 3 = moderate to severe, 4 = severe). Continuous-wave Doppler of the TR jet was used for the estimation of the systolic pulmonary artery pressure (SPAP) using the modified Bernoulli equation and right atrial pressure, which was estimated in consonance with inferior vena cava size.

The left ventricular (LV) ejection fraction (LVEF) was determined according to the Simpson's rule. RV function was evaluated by using several parameters, including tricuspid annular plane systolic excursion (TAPSE), tricuspid lateral annular systolic velocity (S'), and by the RV Tei index (i.e., myocardial performance index). The M-mode apical four-chamber imaging mode was used for the assessment of the TAPSE, wherein the cursor was oriented to the junction of the RV free wall and TV plane. TAPSE was determined by tricuspid annulus displacement from end-diastole to end-systole.[15, 16] Pulsed wave tissue Doppler using the apical four-chamber imaging mode was used for the measurement of RV S'. [17] The RV Tei was calculated by the difference in the interval between cessation and onset of tricuspid flow velocity and the RV outflow velocity time. This difference is then divided by the RV outflow velocity time.[18]

Statistical analysis

Data are presented as numbers and percentages for categorical variables. For continuous variables mean ± standard deviation and median (interquartile range) are shown. Echocardiographic parameters before LP implantation were compared with 12 months follow-up using the Wilcoxon signed-rank test. The binary logistic regression test was used to predict the relationship of potential predictors such as percentage pacing, pacing during echocardiogram, and cardiac dimensions, associated with increased TR.

For the assessment of the intra-observer variability of the primary outcome (i.e., TR), one observer (H.A.C.M) re-evaluated 25 randomly selected echocardiographic studies. The observer was fully blinded, and the interval between initial and reassessment was more than 2 months. For the inter-observer variability, 25 randomly selected echocardiograms were evaluated by fully blinded experienced echocardiographers. The observer variability was assessed by using the two-way mixed intraclass correlation coefficient.

Statistical significance was considered achieved at a p-value <0.05. All statistical analyses were performed using IBM SPSS Statistics for Windows (or Macintosh), Version 24.0 Armonk, NY, IBM Corp.

Results

Study cohort

An overview of the baseline characteristics are displayed in **Table 1**. Pre- and post-implant echocardiographic studies were done in 56 patients who underwent LP implantation between January 2013 and May 2017. In 3 patients the echocardiographic quality was insufficient for the assessment of cardiac and valvular morphology, leaving a final cohort of 53 patients. (**Table 2**)

Table 1. Baseline characteristics

	(n=53)
Age, years	80.5 ± 7.92
Male, n (%)	37 (70%)
BMI * (kg/m^2)	25.4 ± 3.66
Pacing Indication, n (%)	
Bradycardia associated with persistent or permanent atrial tachyarrhythmia	28 (53%)
Sinus node dysfunction	17 (32%)
Atrioventricular block	8 (15%)
Cardiovascular Disease History, n (%)	
Congestive heart failure	5 (9%)
Coronary artery disease	3 (6%)
Hypertension	17 (32%)
Myocardial infarction	2 (4%)
Cardiomyopathy	2 (4%)
Other Comorbidities, n (%)	
COPD †	2 (4%)
Diabetes	6 (11%)
Renal dysfunction	4 (8%)
CVA ‡	2 (4%)
Leadless pacemaker	
Nanostim, n (%)	28 (53%)
Micra, n (%)	25 (47%)

*BMI, body mass index; †COPD, chronic obstructive pulmonary disease; ‡CVA, cerebellar vascular accident

Implantation

In this study population, 28 Nanostim and 25 Micra devices were implanted with adequate electrical parameters. In 42 patients the LP was adequately placed in the RV within 1 deployment. The mean LP procedure duration was 39.4 ± 12.8 minutes. The LP procedure duration was defined as the time from access until removal of the introducer. The device was placed in 42 (79%) patients in the RV apex, in 8 (15%) patients in the apical-septum, and in 3 (6%) patients in the septum of the RV. There was 1 LP recipient who had a complication following the Nanostim procedure. The patient suffered from an arteriovenous fistula at the access site but this did not result in longer hospitalization.

Atrioventricular valve regurgitation

In the total cohort, TR severity was graded as being more severe in 23 (43%), unchanged in 27 (51%) and less severe in 3 (6%) patients (p<0.001) at 12 months after implant. (**Figure 1 and Figure 2)**. More severe TR was observed in 12 (43%) of the Nanostim (p=0.007) and 11 (44%) of Micra recipients (p=0.005) at 12 months compared to baseline. Binary logistic regression revealed that a more RV septal position compared to an apical position of the LP (odds ratio [OR] 5.20, 95% confidence interval [CI] 1.22-22.2, p= 0.03) was associated with worsening TR. In addition, a further distance from the proximal end of the device to the TV based on echocardiography seems to positively impact TV function (OR 0.96, 95% CI 0.92-

1.01, p=0.09). The need for multiple device deployments did not interfere with TV function at last follow-up (OR 1.59, 95% CI 0.40-6.26, p=0.51). In addition, longer procedural time was not associated with new onset or worsening TV dysfunction (p=0.73). There was no significant correlation between the percentage of paced beats and TV competence (OR 1.00, 95% CI 0.98-1.01, p=0.94), and between patients that were paced during follow-up echocardiogram (n=21) and increasing TR (OR 0.63, 95% CI 0.15-2.66, p=0.63). Out of 14 patients that had a pacing percentage of less than 10%, 7 (50%) patients had an increase in TV incompetence. RV (OR 1.01, 95% CI 0.91-1.1, p=0.84) and right atrial dimensions (OR 1.01, 95% CI 0.93 -1.09) did not result in an increase of TR regurgitation. An increase in SPAP did not correlate with worsening TR (OR 1.40, 95% CI 0.37-5.26, p=0.62). Lastly, aggravation of MR was not related to an intensification of TR (OR 0.50, 95% CI 0.15-1.75, p=0.28). The pre- and post-implant echocardiographic assessments of the total cohort are listed in **Table 2**, and separately for the Nanostim and Micra in **Table 3**.

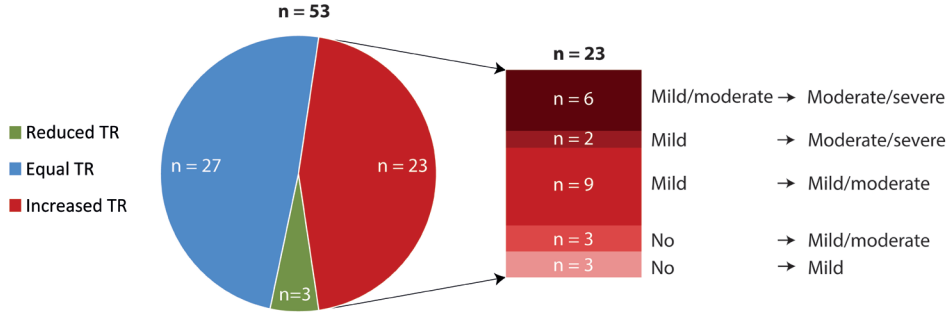

Figure 1. The development of TR in LP recipients. Out of the total cohort, 23 patients had an intensification of TR at 12 months after Nanostim or Micra LP implantation. In 5 patients TR severity was scored 2 gradations higher at follow-up compared to baseline, and in the remaining patients the degree of TR was graded 1 category higher.

The degree of MR was assessed as being more severe in 17 (38%), unchanged in 24 (55%), and less severe in 3 (7%) of cases (p=0.006) at 12 months compared with the pre-implant echocardiogram. The prevalence of new onset or worsening MR was high in patients with a pacemaker rhythm on electrocardiography at the follow-up visit, namely in 57% of cases. The mean percentage of pacing in the group of patients with aggravating MR was higher compared with those with an equal degree of MR (i.e., 48 ± 10% versus 43 ± 7.5%, respectively). There were no significant changes observed in LV end-diastolic volume (92.4 ± 32.9 versus 85.8 ± 25.7 mL, p=0.68) and left atrial volumes (50.6 ± 23.9 versus 48.8 ± 21.6 mL, p=0.84) between the follow-up visit and baseline.

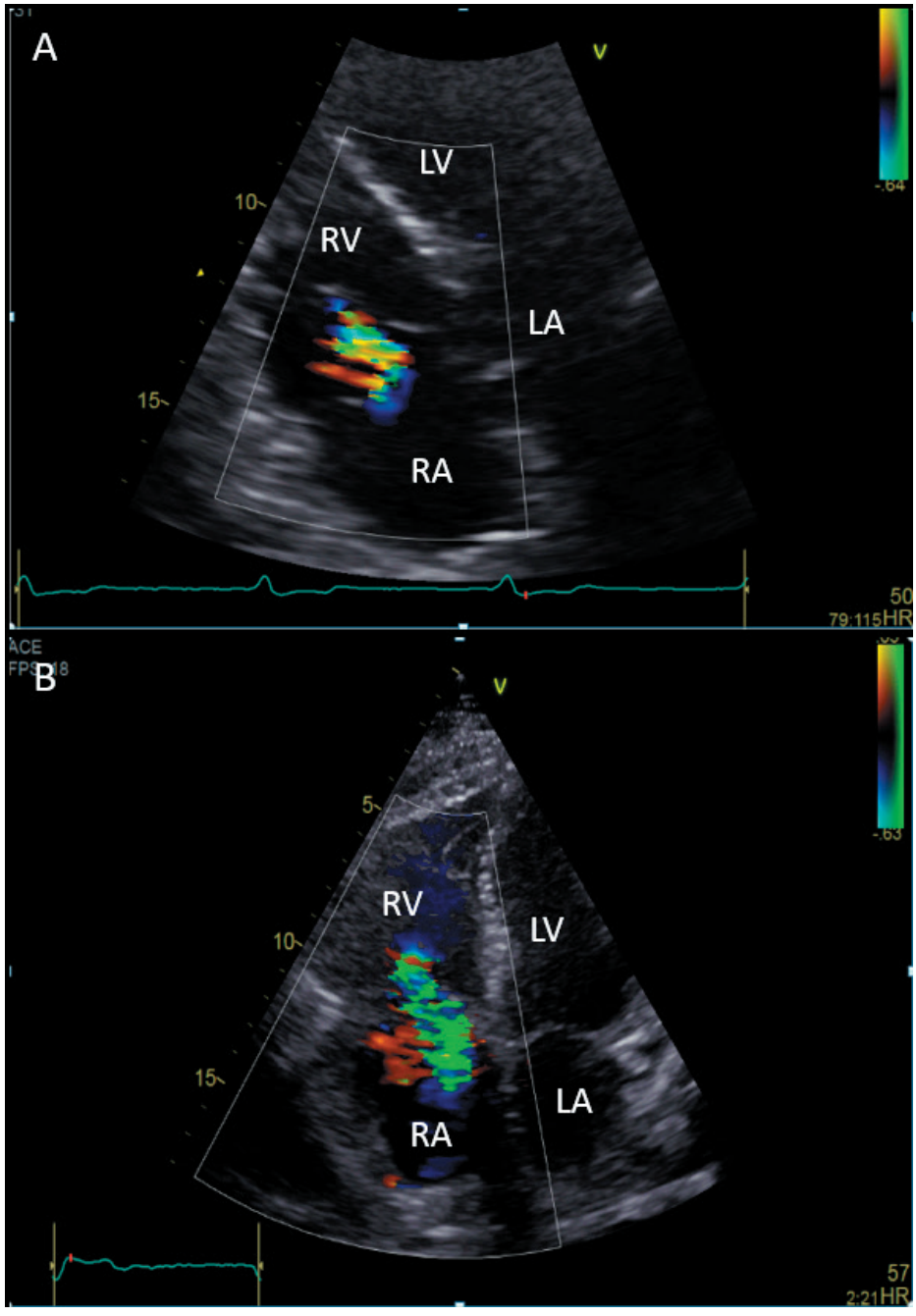

Figure 2. Echocardiographic evaluation of TR severity following LP therapy. Deterioration of tricuspid valve function in a patient following LP therapy. TR severity was evaluated by transthoracic echocardiography at baseline (Panel A) and 12 months post LP implant (Panel B). The baseline echocardiogram illustrates mild TR, whereas moderate/severe TR can be seen in the follow-up echo in this LP recipient. *LA, left atrium; LV, left ventricle; RA, right atrium; RV right ventricle*

Table 2. Echocardiographic indices before and at 12 months after leadless pacemaker implantation (total cohort)

Echocardiographic indices	Before implantation	12 months after implantation	P-value
LV† end-diastolic diameter, mm, mean ± SD	48.6 ± 7.72	48.4 ± 7.31	0.75
LV end systolic diameter, mm, mean ± SD	31.4 ± 7.51	31.8 ± 7.2	0.33
LV end-diastolic septum thickness, mm, mean ± SD	11.4 ± 2.17	10.5 ± 1.66	0.74
LV end-diastolic volume, mL, mean ± SD	92.4 ± 32.9	85.8 ± 25.7	0.68
LV end systolic volume, mL, mean ± SD	43.2 ± 18.1	43.7 ± 16.4	0.29
LV ejection fraction, %, mean ± SD	53.5 ± 8.55	50.2 ± 8.55	0.03
LV TEI, mean ± SD (n=33)	0.48 ± 0.12	0.69 ± 0.27	0.003
LVOT‡ VTI††, cm, mean ± SD (n=47)	21.4 ± 3.70	20.2 ± 5.20	0.37
LA* volume, mL/m2, mean ± SD	50.6 ± 23.9	48.8 ± 21.6	0.84
RV‖ end-diastolic diameter, mm, mean ± SD	42.7 ± 6.26	43.6 ± 5.56	0.10
TAPSE,** mm, mean ± SD	18.6 ± 6.81	16.24 ± 6.52	0.003
S wave, # cm/s, mean ± SD, (n=35)	11.8 ± 3.04	10.9 ± 2.49	0.02
RV TEI, mean ± SD, (n=36)	0.40 ± 0.10	0.50 ±0.16	0.04
sPAP¶, mmHg, mean ± SD	32.3 ± 8.72	32.0 ±8.91	0.21
RA§ area, cm^2, mean ± SD	21.6 ± 6.72	22.4 ±6.79	0.14
Mitral valve disease, (n=44)			
No	9	4	0.006
Mild regurgitation	22	21	
Mild to Moderate regurgitation	11	14	
Moderate to severe regurgitation	2	3	
Severe regurgitation	0	2	
Aortic valve disease, (n=48)			
No	25	22	0.07
Mild regurgitation	20	19	
Moderate regurgitation	3	7	
Severe regurgitation	0	0	
Tricuspid valve disease			
No	6	1	<0.001
Mild regurgitation	26	18	
Mild to Moderate regurgitation	14	20	
Moderate to severe regurgitation	7	14	
Severe regurgitation	0	0	

*LA, left atrium; †LV, left ventricle; ‡LVOT, left ventricular outflow tract; §RA, right atrium; ‖RV, right ventricle; ¶ sPAP, systolic pulmonary arterial pressure; # S wave, derived tricuspid lateral annular systolic velocity; **TAPSE, tricuspid annular plane systolic excursion; ††VTI, velocity time integral

Left and right ventricular function

The Wilcoxon signed-rank test revealed that TAPSE (p=0.003) and RV S' (p=0.02) significantly decreased. The RV Tei index increased significantly following LP implant (p=0.04). An LVEF reduction (p=0.03) and an increase in LV Tei (p=0.003) were observed at 12 months compared to pre-LP placement. In 11 (34%) patients, the LVEF decreased more than 10%. The percentages of pacing in these patients were as follows: 5 had 100% pacing, 1 had 89% pacing, 1 had 60% pacing and 4 patients had a pacing percentage of less than 20%.

Table 3. Echocardiographic indices before and at 12 months after leadless pacemaker implantation (Nanostim and Micra separately).

Echocardiographic indices	Nanostim			Micra		
	Baseline	12 months	P-value	Baseline	12 months	P-value
LV† end-diastolic diameter, mm, mean ± SD	49.9 ± 7.32	50.2 ± 6.73	0.55	47.1 ± 8.30	46.8 ± 7.51	0.79
LV end systolic diameter, mm, mean ± SD	32.6 ± 6.83	33.4 ± 6.72	0.48	30.2 ± 8.09	30.2 ± 7.29	0.46
LV end-diastolic septum thickness, mm, mean ± SD	11.2 ± 2.20	11.3 ± 1.61	0.88	11.7 ± 2.05	12.0 ± 2.49	0.77
LV end-diastolic volume, mL, mean ± SD	93.2 ± 32.2	90.5 ± 24.4	0.95	91.2 ± 35.1	82 ± 28.7	0.19
LV end systolic volume, mL, mean ± SD	43.3 ± 17.8	45.4 ± 14.8	0.14	43.1 ± 19.2	43.1 ± 19.8	1.00
LV ejection fraction, %, mean ± SD	54.1 ± 8.56	50.3 ± 7.48	0.01	52.6 ± 9.77	50.2 ± 9.93	0.68
LV TEI, mean ± SD	0.48 ± 0.13	0.66 ± 0.26	0.05	0.48 ± 0.11	0.74 ± 0.29	0.03
LVOT‡ VTI††, cm , mean ± SD	20.2 ± 3.83	20.1 ± 4.25	0.71	22.8 ±3.11	20.9 ±6.53	0.32
LA* volume, mL/m2, mean ± SD	54.8 ± 24.8	50.9 ± 18.1	0.88	44.91 ± 22.2	48.3 ± 27.3	0.97
RV‖ end-diastolic diameter, mm, mean ± SD	42.1 ± 6.65	43.2 ± 5.19	0.14	43.7 ± 5.67	44.1 ± 6.23	0.48
TAPSE**, mm, mean ± SD	19.9 ± 4.54	18.2 ± 4.33	0.01	16.8 ± 8.64	14.1 ± 7.81	0.08
S wave#, cm/s, mean ± SD	11.4 ± 3.23	11.2 ± 2.07	0.31	12.4 ± 2.81	10.6 ±3.11	0.01
RV TEI, mean ± SD	0.42 ± 0.10	0.48 ±0.14	0.44	0.36 ± 0.08	0.52 ± 0.19	0.04
sPAP¶, mmHg, mean ± SD	31.7 ± 10.1	31.6 ± 5.96	0.83	33.1 ± 6.70	32.5 ± 11.6	0.05
RA§ area, cm^2, mean ± SD	22.3 ± 6.34	23.2 ± 5.91	0.23	20.7 ±7.19	21.4 ± 7.75	0.39
Mitral valve disease						
No	4	2	0.005	5	2	0.37
Mild regurgitation	12	8		10	13	
Mild to Moderate regurgitation	4	7		7	7	
Moderate to severe regurgitation	1	2		1	1	
Severe regurgitation	0	2		0	0	
Aortic valve disease						
No	13	13	1.00	12	9	0.02
Mild regurgitation	12	12		8	7	
Moderate regurgitation	1	1		2	6	
Severe regurgitation	0	0		0	0	
Tricuspid valve disease						
No	4	0	0.007	2	1	0.005
Mild regurgitation	11	9		15	9	
Mild to Moderate regurgitation	7	11		7	9	
Moderate to severe regurgitation	6	8		1	6	
Severe regurgitation	0	0		0	0	

*LA, left atrium; †LV, left ventricle; ‡LVOT, left ventricular outflow tract; §RA, right atrium; ||RV, right ventricle; ¶ sPAP, systolic pulmonary arterial pressure; # S wave, derived tricuspid lateral annular systolic velocity; **TAPSE, tricuspid annular plane systolic excursion; ††VTI, velocity time integral

Observer variability

For the intra-observer variability measurements, the correlation for TR was 0.84 (95% confidence interval [CI] 0.64-0.93, p< 0.001). For the inter-observer assessments, the correlation for TR was 0.86 (95% CI 0.67-0.94, p<0.001), for MR was 0.93 (95% CI 0.85-0.97, p<0.001), for LV end-diastolic diameter was 0.96 (95% CI 0.91-0.98, p<0.001), for RV end-diastolic diameter was 0.90 (95% CI 0.70-0.96, p<0.001), for right atrial area was 0.94 (95% CI 0.85-0.98, p<0.001), and for TAPSE was 0.94 (95% CI 0.83-0.98, p<0.001).

Discussion

The current study elicited several major findings. To our knowledge, this is the first and largest study to document intensification of TR following Nanostim and Micra LP therapy. Our data suggest that the mechanical impact of the device near the TV apparatus is the most likely cause of this phenomenon because –the recommended- more septal position of the LP was associated with an increase in TV incompetence. In addition, other factors such as procedural characteristics, pacing percentage, paced rhythm during echocardiogram, and changes in SPAP, MR, and cardiac morphology played no significant role in the worsening of TR. We further observed that LP implantation was associated with an aggravation of MR, RV and LV dysfunction through 12 months' follow-up, which may be a result of RV pacing-induced ventricular dyssynchrony.

Atrioventricular valve regurgitation

Conventional defibrillator and PM leads need to be placed across the TV, which can result in a degree of iatrogenic TR. TR is independently related to an increasing prevalence of mortality and heart failure hospitalization, even after accounting for well-known causes of TR such as left-sided heart failure and RV dilation.[4,19] Studies show that in patients with cardiac implantable electronic devices, the prevalence of new onset or worsening TR increases with 20 to 50 percent compared to patients without a PM. [1,2] LP therapy is a promising approach of cardiac pacing, consisting of a miniaturized device completely placed inside the RV. It has been suggested that the absence of a transvalvular lead potentially reduces inadequate leaflet coaptation and mechanical impact on the TV apparatus. The immediate impact of leadless pacing on cardiac function and TR based on echocardiography has been studied by Salaun and co-workers.[20] They concluded that there were no significant changes in cardiac morphology and function, including TR and MR at 2 months following LP implantation. There are differences between Salaun *et al.* - and this study that should be emphasized. Their study cohort involved 23 patients, whereas we included 53 patients. Moreover, their echocardiographic assessments were performed 2 months following the LP procedure, whereas our echocardiographic studies were obtained at 12 months follow-up. In contrast, this study demonstrated that LP therapy is associated with an aggravation of TR and MR severity. Four potential mechanisms are

involved in TV dysfunction following LP implantation: 1) TV damage during implantation, 2) on-going mechanical impact of the device on the TV or its subvalvular apparatus, 3) pacing-induced RV dyssynchrony, or 4) other factors. 1) There are several TV complications that may occur during the LP implant procedure including leaflet perforation, chordal tearing and papillary muscle injury.[4] One can argue that multiple device deployments and longer manipulation of the device before reaching adequate electrical parameters may increase the risk for surgical injury to the TV apparatus, but neither procedure duration nor multiple device manipulations at implant were associated with an increase in TV incompetence. Moreover, Salaun and colleagues observed no significant TV dysfunction in 23 patients studied 2 months after LP implant [20]. Their data, combined with our observations, suggest that LP-related TV dysfunction is not typically an acute complication of the implant procedure; it may take some time to develop. 2) Our data suggest that mechanical interference of the LP device with the TV subvalvular apparatus may be the primary cause of worsening TR over time. Patients with a more septal position of the LP were 5 times more prone to worsening TR. Encapsulation of the LP may result in loss of leaflet mobility or coaptation due to adhesive interactions between fibrotic tissue around the device and subvalvular endocardial structures. 3) The role of RV pacing itself using conventional transvenous leads in causing TR has been controversial.[21] The majority of conventional PM studies demonstrated that the number of paced beats does not relate with worsening TR.[22-24] Whereas others have suggested that pacing-induced dyssynchrony may result in secondary TR.[25,26] In line with previous studies evaluating TV dysfunction following lead-based PM therapy, we demonstrated that the percentage of RV pacing did not correlate with new onset or worsening TR. This was confirmed by the fact that in the group of patients with lowest pacing percentages, therefore excluding pacing-induced TR, the prevalence of TR aggravatation was common. Furthermore, patients that were paced during the follow-up echocardiogram were not more prone to the development of TR in the current cohort. 4) There are several potential secondary causes of TV insufficiency, such as the development of pulmonary artery hypertension, RV dilatation, left-sided heart valve disease or heart failure, and chronic lung disease.[4] TR development did not appear to result from any of these factors in the current study. This suggests that the LP by itself results in primary new onset or worsening TR.

In addition to TR aggravation, we observed an increase in prevalence of MR following LP placement. The majority of patients with new onset or worsening MR had a paced rhythm on electrocardiography at the follow-up visit, which might be an explanation for this observation. Although the pacing percentage was higher in the worsening MR group compared to the equal MR group, it reached no statistical significance. Therefore, it does not permit us to draw definite conclusions on the primary cause of the increase in MV incompetence. However, it has been shown in conventional PM cohorts that dyssynchronous LV electromechanical activation induced by RV pacing results in mitral

annular dilatation and anomalous leaflet coaptation which is responsible for causing MR.[24,27-29]

Left and right ventricular function

Multiple studies have evaluated the impact of lead-based RV pacing on cardiac function. [30-33] Several studies suggested that pacing-induced mechanical dyssynchrony is associated with occurrence or worsening of left-sided heart failure and hospitalization, especially in heart failure patients.[34] In contrast, Alizadeh *et al.* documented that the LV function remained in normal limits in PM patients with a preserved ejection fraction at baseline through 4 years' follow up. [21] We found a significant LVEF reduction of 3.2%. One may argue what the clinical relevance of this observation is. Yet, we showed that in one patient new onset reduced LVEF (i.e., <40%) developed following LP implantation with a follow-up of 12 months. Furthermore, a substantial reduction in LVEF (i.e., >10% reduction) was not uncommon in our study population, yet no patients developed symptoms of LV dysfunction. Our data further showed that there was a significant reduction in RV function following LP implantation. There are several mechanisms that are involved in potential harmful effects of RV pacing on cardiac function. In general, both the electrical and mechanical activation patterns of the ventricles are changed during RV pacing which result in less effective ventricular contraction and subsequently in a reduction of cardiac output. [3,10] Furthermore, dyssynchronous RV and LV electromechanical activation may induce changes in coronary blood flow, hemodynamics, remodeling, perfusion and metabolism which may lead to worsening heart function.[3,10] To date, it remains unknown why some patients acutely develop pathological dyssynchrony after RV pacing, and why others are spared.[10]

Limitations

The current study has some limitations. Firstly, in this single-center study LP implantations were performed by two operators. Data on heart structure and function following LP therapy from different institutions and operators are required to determine validity of the present results. Secondly, the immediate impact of LP placement on TV function was not assessed as no echocardiogram was performed prior to discharge. Therefore, iatrogenic damage to the TV could have been missed. However, procedural characteristics such as longer manipulation of the device and number of device deployments were not associated with intensification of TR. Thirdly, echocardiographic evaluation of RV and TV morphology and function remains challenging. Yet, echocardiography is the first choice of diagnostic tools in the follow-up of these patients. Lastly, a direct comparison of cardiac and atrioventricular valve function between lead-based PMs and LPs was not performed due to single-arm study design.

Conclusion

LP therapy is associated with an aggravation of TR severity at 12 months follow-up, despite the circumvention of transvalvular leads. Our data suggest that the mechanical interference of the device on the TV or its subvalvular apparatus is the primary cause, as a more septal position was correlated with an increase in TV incompetence. We further observed a decrease in MV and biventricular function, which may be a consequence of abnormal electrical and mechanical activation patterns of the ventricles induced by LP therapy. These results are highly relevant as they contradict expected performance of LP therapy, and warrants further investigation.

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none

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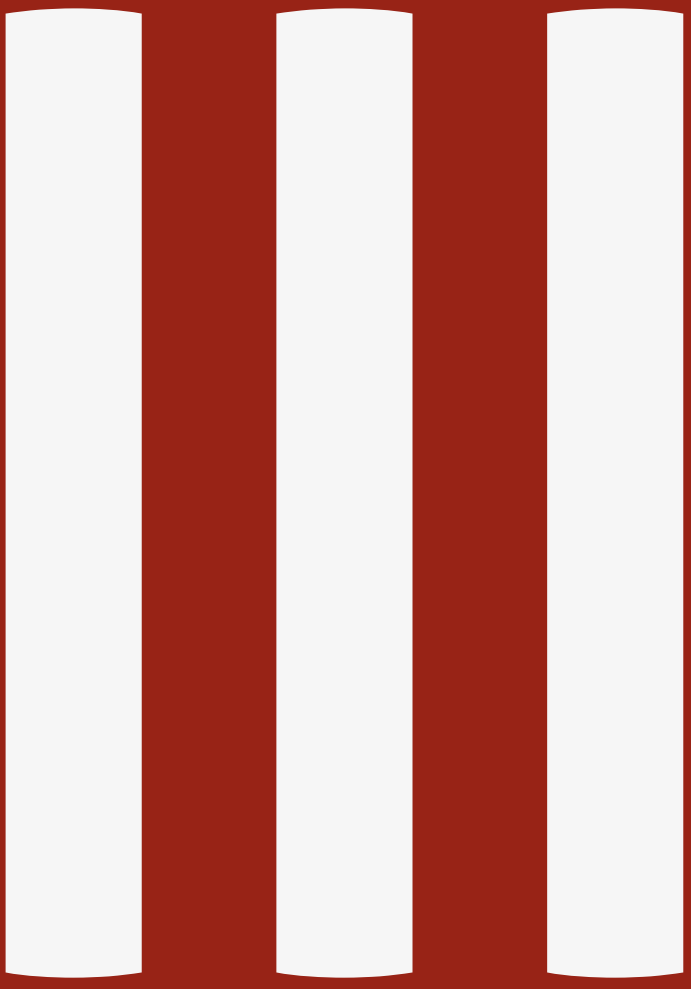
Supplementary File

Table 1.

Echo parameter	Interclass correlation	95% confidence interval	p-Value
Mitral valve regurgitation	0.93	0.85-0.97	<0.001
Aortic valve regurgitation	0.83	0.59 – 0.93	<0.001
Trispuspid valve regurgitation	0.86	0.67-0.94	<0.001
LV end-diastolic diameter	0.96	0.91-0.98	<0.001
LV end-diastolic septum	0.78	0.42-0.91	0.001
LV ejection fraction	0.94	0.86-0.98	<0.001
LV outflow tract	0.82	0.52-0.93	<0.001
LA volume	0.98	0.96-0.99	<0.001
RV end-diastolic diameter	0.90	0.70-0.96	<0.001
Right atrial area	0.94	0.85-0.98	<0.001
TAPSE	0.94	0.83-0.98	<0.001
S wave	0.91	0.78-0.97	<0.001
sPAP	0.93	0.81-0.97	<0.001

LA, left atrial; LV, left ventricular; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion

PART



Novel pacing approach and thesis summary

CHAPTER

Feasibility of an Entirely Extracardiac, Minimally Invasive, Temporary Pacing System

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Background A completely extracardiac pacing system provides the potential for clinical advantages over existing device alternatives that require intravascular, endocardial or epicardial contact. Preliminary studies evaluating the feasibility of cardiac pacing with a lead in the anterior mediastinum, outside the pericardium and circulatory system have been completed. Specifically, examining (1) the anatomic access route, (2) usability of a delivery tool to facilitate lead placement and (3) extracardiac pacing performance.

Methods Feasibility evaluations included (1) a retrospective CT analysis to characterize anatomic variations related to lead access, (2) accessing the anterior mediastinum in cadavers and human subjects using a custom delivery tool (figure) and (3) acute clinical pacing performance.

Results Major findings: (1) A total of 166 (95%) out of 174 patients had a viable lead access path through the 4^{th}, 5^{th} or 6^{th} intercostal space. (2) Access to the targeted implant location using a delivery tool was successful in all 5 cadavers and 3 humans without use of fluoroscopy and with an average lead delivery time of 121 ± 52 seconds. No damage to the lung, pericardium, heart or internal thoracic vessels occurred. (3) Pacing performance was tested in 6 human subjects showing a threshold voltage of 4.7V (2.7-6.7), threshold pulse width of 1.8 ms (1.0-2.5) and an impedance of 1,205 Ω (894-1,786). R-wave amplitudes measured 9.6 mV (5.6-12.0).

Conclusion Results support the feasibility for this completely extracardiac pacing method in a heterogeneous patient population, using a minimally invasive delivery approach and with adequate sensing and thresholds suited for temporary pacing.

Journal Subject terms/keywords: Cardiac Pacing; Extracardiac; Delivery Tool; Temporary; Permanent; Cardiac Notch; Anterior Mediastinum

Abstract

Introduction

Permanent transvenous pacemaker (PM) systems involve the placement of one or more leads in or on the heart, which are connected to an implantable pulse generator. While these systems provide an important life-sustaining therapy for patients with bradycardia, they are not without risk. Lead and pocket issues result in relevant complication rates in conventional PM recipients.[1] Recently, leadless pacemaker (LP) therapy has been introduced as a therapeutic alternative to avoid these well-known complications of conventional PM therapy.[2, 3] Despite promising results, important challenges remain with LP therapy such as the optimal end-of-life strategy and the occurrence of life-threatening cardiac perforations.[4, 5]

Temporary transvenous cardiac pacing therapy is widely used to correct compromising or life-threatening arrhythmias in acute settings. Yet, complications are common in patients treated with transvenous temporary pacing, and have remained high since its introduction six decades ago.[6-8]

A novel, completely extracardiac pacing system is being developed that can deliver bradycardia pacing therapy, while avoiding risks and complications associated with pacing systems that require intravascular, endocardial or epicardial contact. Such an extracardiac pacing system [Atacor Medical, Inc., San Clemente, CA ("AtaCor")] includes a lead within the anterior mediastinum through an intercostal space over the cardiac notch of the left lung, using a custom developed delivery tool, which can be attached to an external or permanent pulse generator system (Figure 1). This novel approach has the potential to become a viable pacing option in challenging clinical situations, such as acute temporary pacing, device infection, children, congenital heart disease and venous obstruction. This approach may also provide a favorable alternative for patients in whom transient or permanent pacing needs develop as a result of other interventions (e.g. transcatheter aortic valve replacement (TAVR)) or emergent cardiovascular circumstances where time is essential and fluoroscopy is not.

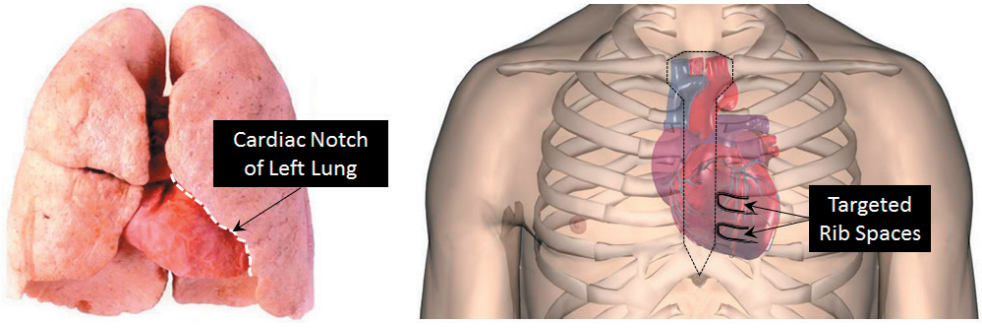

Figure 1 . (Left) Cardiac notch of the left lung provides left parasternal access into the anterior mediastinum towards the heart without lung obstruction. (Right) Targeted rib spaces for lead insertion over the cardiac notch of the left lung.

This manuscript compiles several preliminary studies demonstrating the conceptual foundation and feasibility of an innovative and radically different cardiac pacing concept and is presented in three sections: 1) A computed tomography (CT) evaluation of the anterior mediastinum and its access through the intercostal space in a large heterogeneous patient population to characterize potential candidates, 2) An evaluation of the ability to gain access and deploy a substernal lead using the delivery tool in a cadaver model and human subjects and 3) Cardiac pacing performance in the anterior mediastinum in humans.

Methods

To evaluate feasibility of extracardiac pacing in the anterior mediastinum, three separate studies were performed, each designed to assess specific aspects of this novel pacing approach and system. First, access to the anterior mediastinum was analyzed in a retrospective CT study. Secondly, performance of the delivery tool was evaluated using both a cadaver model and human subjects. Finally, ventricular pacing capture, R-wave sensing and muscle stimulation were tested in an acute human study. Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to AtaCor Medical, Inc. at alan@atacor.com.

The intended implant technique of the final system envisions placement of a pacing lead through an intercostal space, near the left sternal margin, over the cardiac notch of the left lung (Figure 1). The distal end of the lead is equipped with a pair of closely spaced electrodes that are non-circumferential and oriented towards the heart, a design feature intended to minimize the potential for intercostal skeletal muscle stimulation. The distal end of the lead is designed to reside within the connective tissue between the posterior surface of the anterior chest wall and the pericardium. Leads will be designed for removal by direct, manual retraction force, i.e., pulling the lead, similar to the method used for current subcutaneous ICD leads. .

1. Anatomic evaluation of the human anterior mediastinum.

This study was designed as a retrospective CT analysis to characterize the substernal space within the anterior mediastinum in four specific patient populations, namely a broad population of control patients (arm A), patients with pulmonary disease (arm B), patients with congenital heart disease (arm C) and patients with an implanted transvenous pacemaker (PM) or implantable cardioverter (ICD) system (arm D). Specifically, the substernal space of interest, is defined as the portion of the anterior mediastinum between the intercostal muscle/sternum and the outer surface of the pericardium (Figure 2). Rib numbers were identified on sagittal CT views to visualize the 4th, 5th and 6th left

intercostal spaces (ICS). The path through the ICS near the left sternal margin was assessed for obstruction by the left lung. Additional CT measurements and analysis were performed to characterize the anatomy within, and adjacent to, the anterior mediastinum where the substernal pacing lead is planned to be implanted (supplemental material).

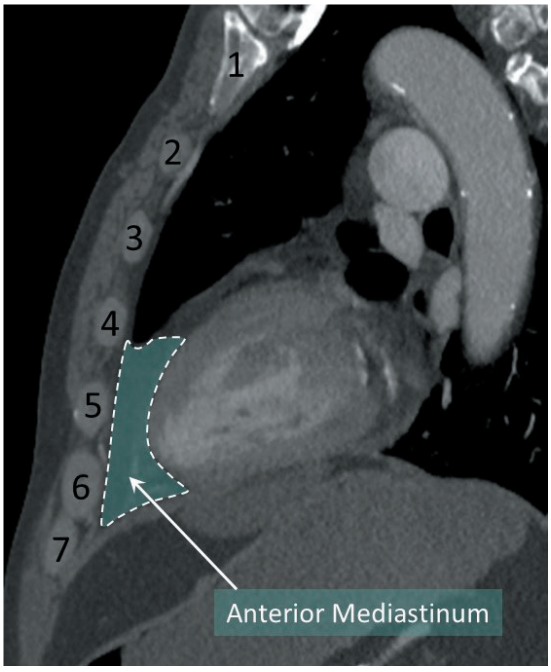

Figure 2. Sagittal CT view with targeted location, the anterior mediastinum within the cardiac notch, for pacing.

2. Evaluation of the custom lead delivery tool.

This analysis was designed to evaluate the ability to access the anterior mediastinum using prototype lead delivery tools (Figure 3). Initially, three cadavers and three human subjects were tested with a first-generation delivery tool prototype (Figure 3 left). Subsequently, two more cadavers were tested with a second-generation custom delivery tool (Figure 3 right). X-rays and CT imaging of the later unpreserved cadavers were acquired two days prior to the implant procedures and were analyzed according to the above described methods in the CT study. Each use of the delivery tool and all implants were performed by a practicing clinical electrophysiologist. Post-procedure dissections were performed on the cadaver subjects to characterize any anatomical damage that may have resulted from the implant procedure. Additionally, the first-generation delivery tool was evaluated for safety in live subjects undergoing valve or septal defect open heart surgery. In that clinical evaluation, the custom delivery tool was used to access the anterior mediastinum prior to performing the median sternotomy for the patients' surgical index procedure. Damage to adjacent mediastinal tissue was also assessed post sternotomy.

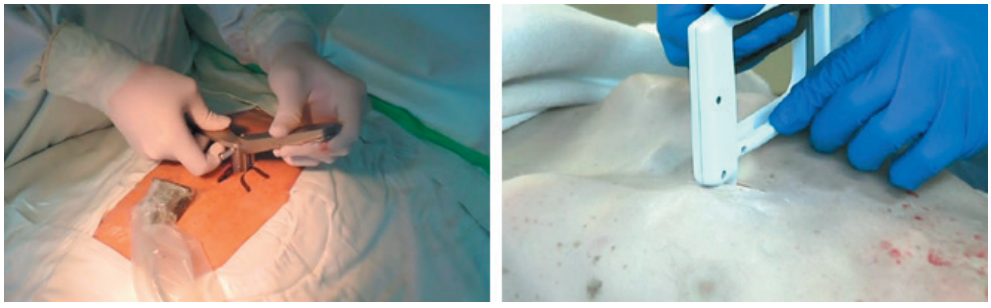

Figure 3. First (left) and second (right) generation delivery tools to facilitate lead placement into the anterior mediastinum.

Study Devices

The first- and second-generation delivery tools are both equipped with a pair of blunt-tipped separating access tips which are used to access the anterior mediastinum. The delivery tools are intended to be directed along the surface of the sternum from the midline to the left sternal margin until they are pushed into the anterior mediastinum via the target rib space. The access tips are then separated using a built-in lever, creating an access channel within which a substernal lead is inserted. The delivery tools are then removed, leaving the substernal lead in place (Figure 4). Detailed description of the delivery tools is provided in the supplemental material.

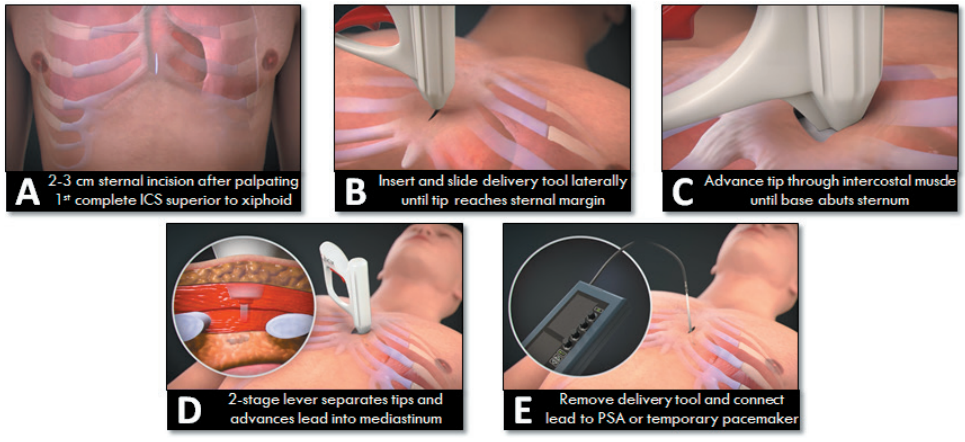

Figure 4. **(A)** Access to the anterior mediastinum is gained over the cardiac notch of the left lung near the sternal margin through ICS 4, 5 or 6. **(B-C)** The delivery tool is applied to the surface of the sternum through a 2-3 cm skin incision and then moved laterally to find the sternal margin. The delivery tool tip is then advanced through the intercostal muscle into the anterior mediastinum. **(D)** Squeezing the delivery tool lever advances the substernal lead into position. (E) The delivery tool is removed leaving the substernal lead in place which can be attached to a temporary or permanent pacing system.

Study Procedure

The delivery tool is intended to be positioned using anatomical landmarks, without the need for fluoroscopic guidance to locate a suitable entry point into the anterior

mediastinum. Once access is gained, the delivery tool is used to deploy a pre-loaded substernal lead into position.

3. Human Feasibility Study for Anterior Mediastinum Cardiac Pacing

This study was designed to evaluate cardiac pacing thresholds while pacing intraoperatively using a substernal lead. In addition, the study was designed to characterize the degree of skeletal muscle stimulation while pacing over a range of voltage and pulse widths outputs with a substernal lead. A three-axis accelerometer was placed within a sterile sleeve and adhered to the surface of the anterior chest wall. The accelerometer was sufficiently sensitive to detect mechanical deflections resulting from intrinsic cardiac contractions, a phenomenon that could be visually observed in the accelerometer signals recorded during baseline intrinsic activity. Transcutaneous pacing was then delivered as it is a pacing modality known to elicit substantial skeletal muscle stimulation. Accelerometer signals recorded during transcutaneous pacing clearly demonstrated the skeletal muscle contractions on all three accelerometer axis signals coincident with delivery of transcutaneous pacing stimuli. To demonstrate concept feasibility, non-circumfrential electrodes from commercially available pacing leads were utilized. Two separate leads were equipped with one electrode positioned at the distal end of each lead so that they may be oriented towards the heart. Electrodes were placed in close proximity to each other to facilitate bipolar pacing and sensing. Leads were either manually manipulated with the assistance of a sterile L-shaped bracket or positioned through an early prototype of a custom delivery tool. The study was approved by a reviewing ethics committee for the investigational site. Eligible subjects providing written informed consent were enrolled in the study. All protocol testing occurred intraoperatively. No chronic follow-up visits were required other than to identify any latent clinically adverse events that may have occurred after hospital discharge prior to study exit. For safety purposes, all clinically adverse events were required to be reported. From an effectiveness perspective, targeted intercostal spaces were identified via palpation and confirmed with fluoroscopy. Baseline data, consisting of ECG and 3-axis accelerometer signals were recorded prior to the delivery of any pacing. Signals were collected while delivering 200 mA transcutaneous pacing across the thorax, a control and standard of care known to elicit substantial skeletal muscle stimulation. Substernal leads were placed via (1) a sternal opening, post-sternotomy under the targeted intercostal spaces or (2) directly through the intercostal muscles of the targeted intercostal spaces (Figure 5). Skeletal muscle stimulation tests were then repeated to characterize the degree of skeletal muscle stimulation that occurred in response to substernal compared to cutaneous pacing. Pacing was delivered between two hemispherical electrodes placed in the connective tissue between the sternum and pericardium and oriented towards the heart. Cardiac pacing thresholds were identified and pacing at the threshold voltages, 2x threshold voltage and at 18V was delivered to measure and record the degree of any concomitant skeletal muscle stimulation.

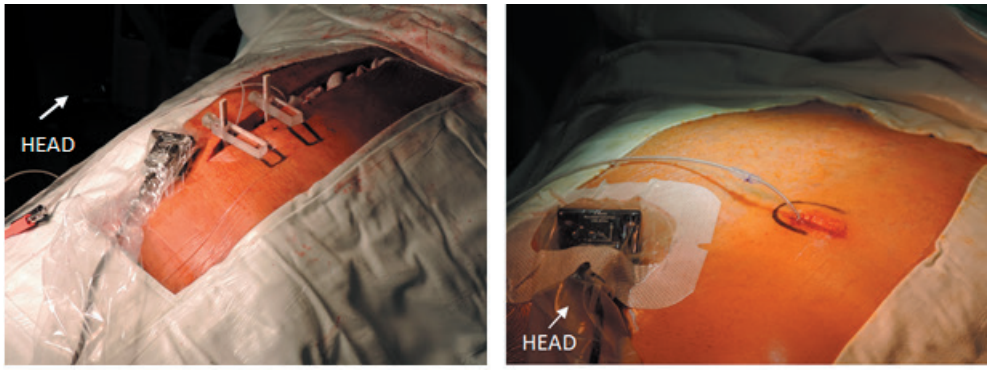

Figure 5. Subject with two substernal leads placed through a sternotomy opening (left) and a different subject (right) with one substernal lead placed using the delivery tool after identifying a targeted intercostal space via palpation (without fluoroscopy).

Statistical Analysis

Continuous variables were tested for normality. Values are presented as means with standard deviations or median with interquartile ranges. Dichotomous data are presented as proportions.

Results

Anatomic evaluation of the human anterior mediastinum.

A total of 174 patients were enrolled in the anatomy study. Arm A, B, and D each included 50 patients, and 35 patients were included in Arm C. Eleven patients were patients with PM devices and with a history of pulmonary disease, therefore these patients were included both in arm B and D for analysis. Baseline characteristics are described in **Table 1**.

The results showed that the anterior mediastinum could be accessed in 166 (94%) of 174 subjects through at least one parasternal point of entry at the level of the 4th, 5th or 6th intercostal space, without contacting the left lung or internal thoracic vein/artery. Eight subjects with COPD appeared to have a lung-obstructed path through all three of the evaluated ICSs; however, 84% of COPD subjects had one or more viable paths through the 4^{th}, 5^{th} or 6^{th} ICS (**Table 1**). The distance between the posterior sternum and pericardium, which is highlighted in Figure 2 was measured in all subjects (Table 1). Additional measurements of the area of interest are reported in the supplementary material.

Table 1. Baseline characteristics and results of CT anatomy study.

	Arm A (n = 50)	Arm B (Lung) (n = 50)	Arm C (CHD) (n = 35)	Arm D (DEVICE) (n = 50)
Baseline characteristics				
Age, years	65.6 ± 11.1	70.7 ± 7.5	40.5 ± 13.6	74.7 ± 7.5
Male, n	25 (50%)	26 (52%)	17 (49%)	24 (48%)
BMI, kg/m^2	29.0 ± 6.3	28.5 ± 8.4	25.9 ± 5.3	28.0 ± 7.2
Device Type				
DDD-PM				32 (64%)
CRT-D				5 (10%)
CRT-P				5 (10%)
DR-ICD				4 (8%)
VR-ICD				2 (4%)
VVI-PM				2 (4%)
Congenital Heart Defect				
Left-sided lesions			14 (40%)	
TGA			9 (26%)	
Tetralogy of Fallot			6 (17%)	
Other			5 (14%)	
Fontan Circulation			1 (3%)	
Lung Disease				
COPD		(66%)		
Asthma		(16%)		
Emphysema		(8%)		
Sarcoidosis		(6%)		
CT analysis Results				
Unobstructed Path to the Anterior Mediastinum				
4th ICS	40 (80%)	27 (54%)	30 (86%)	40 (80%)
5th ICS	49 (98%)	35 (70%)	35 (100%)	45 (90%)
6th ICS	50 (100%)	42 (84%)	35 (100%)	48 (96%)
Unobstructed Path to the anterior mediastinum through any ICS	100%	42 (84%)	35 (100%)	48 (96%)
Distance posterior sternum to pericardium, mm				
4th ICS	5.4 ± 2.5	11.3 ± 8.9	4.6 ± 4.4	6.1 ± 4.3
5th ICS	5.4 ± 3.4	9.2 ± 8.2	3.6 ± 1.5	5.0 ± 2.9
6th ICS	5.9 ± 7.6	9.6 ± 8.1	4.3 ± 2.3	5.2 ± 3.3

COPD = chronic obstructive pulmonary disease, CRT = cardiac resynchronization therapy, ICD = implantable cardioverter-defibrillator, ICS = intercostal space, TGA = transposition of great arteries, PM = pacemaker

Evaluation of the Custom Delivery Tools.

First-generation delivery tool usage was evaluated in three cadavers, followed by three male clinical subjects, aged 19 to 61 (BMI 23.2 - 27.6 m/kg^2), for safety, lead placement and lead delivery time. Lead placement into the anterior mediastinum using the delivery tool without fluoroscopy was successful in all cadavers and subjects. Access to the anterior mediastinum was gained parasternally via the 4th, 5th or 6th left intercostal spaces. There were no instances of damage to the lung, pericardium, heart, internal thoracic vessels or other anatomic structures during post-procedural cadaver assessment and there were no clinically adverse events related to the device or implant procedure. Lead tips were over the right ventricle in all cases and mean lead delivery time was 121 ± 52 seconds,

ranging from 42 seconds to 3 minutes and 38 seconds in the human subjects. Second-generation delivery tool usage was evaluated in two cadavers with successful access to the anterior mediastinum in both cases without the use of fluoroscopic guidance. There was no evidence of damage to the lung, pericardium, heart, internal thoracic vessels or other anatomic structures.

Substernal Cardiac Pacing Results.

Six males (19 to 68 years, BMI 23.2 - 34.9 kg/m^2) were evaluated during valve or septal defect sternotomy surgery. Cardiac capture with substernal leads placed in the anterior mediastinum was achieved in all subjects without any adverse events. The mean and range for threshold voltage, threshold pulse width, impedance and current were 4.7 V [2.7 – 6.7], 1.8 milliseconds [1.0 – 2.5], 1,205 Ω [894 – 1,786] and 4.4 mA [1.7 – 7.3]. Mean and range for R-wave amplitudes were 9.6 [5.6 – 12.0 mV] (Figure 6).

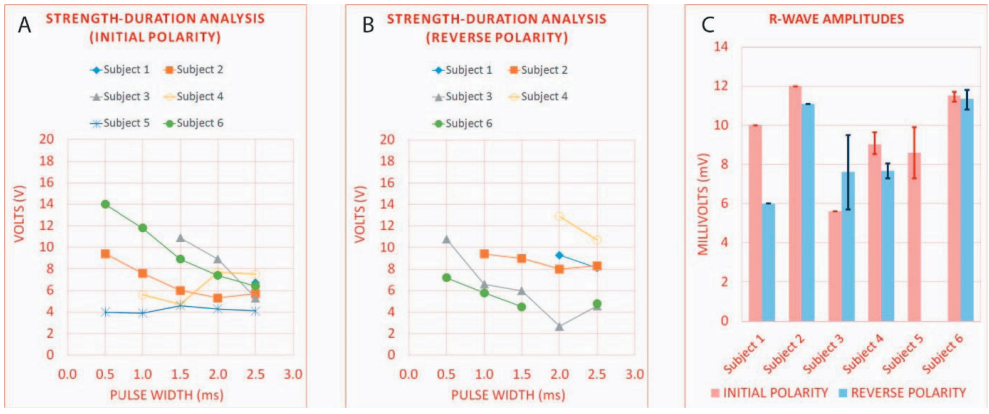

Figure 6. (A) Strength-duration relationships: Initial polarity. **(B)** Strength-duration relationships: Reverse polarity. **(C)** Measured R-wave amplitudes. Error bars = min/max.

Observations from accelerometer recordings and a concomitantly recorded ECG signal clearly demonstrated that there was no change in the morphology of any of the three accelerometer axis signals. This lack of change, independent of pacing with the evaluated lead, supports that pacing did not result in concomitant skeletal muscle stimulation. Skeletal muscle stimulation was clearly detected while delivering transcutaneous pacing. While delivering substernal pacing, no skeletal muscle stimulation was measured over the entire range of electrical outputs (Figure 7). Additionally, palpation of the thorax confirmed the absence of skeletal muscle stimulation while pacing via the substernal leads. In the current studies, which were all acute studies, lead removal was performed with direct retraction without any damage to surrounding tissue.

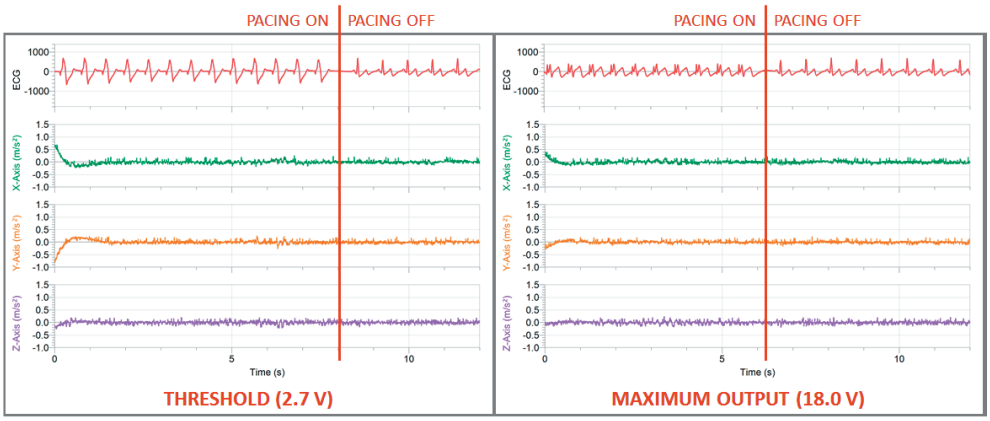

Figure 7. Top tracings in all panels are ECG signals. Lower three signals in all panels are x-, y- and z-axes of an accelerometer placed on the surface of the chest. Panel A: Skeletal muscle stimulation is clearly apparent for the initial 8 seconds of transcutaneous pacing @ 200 mA, after which pacing is turned off. Panel B: No skeletal muscle contraction/movement occurred while pacing with the extracardiac lead at 2.7V. This is supported by the unchanging accelerometer signals before and after pacing is delivered. Panel C: Extracardiac lead pacing at maximum output also resulted in the absence of skeletal muscle contraction/movement, which is supported by the unchanging accelerometer signals before and after pacing is delivered.

Discussion

Major Findings

This collection of feasibility studies describes a novel pacing system that provides cardiac pacing without entering the vascular or pericardial space. Analysis of CT images provided evidence that substernal PM lead placement is applicable for a large range of anatomical variations and medical histories, including patients with pulmonary disease, congenital heart disease, and PM and ICD recipients. In addition, substernal leads can be placed safely and efficiently into the anterior mediastinum in rapid sequence using a custom delivery tool without fluoroscopy. Furthermore, the acute human study demonstrated that substernal pacing was possible without inducing concomitant skeletal muscle stimulation in all subjects. The intention for this novel technology is to first develop a system that can provide temporary pacing in a manner that does not require placement of any devices within the circulatory system.

Analysis of the 174 CT images show that the thickness of the connective tissue in the anterior mediastinum varies, and the average thickness is approximately 5 mm and 10 mm in subjects without and with a history of lung disease, respectively. Available clinical data is limited (n=6) and quantitative analysis of the connective tissue thickness and pacing thresholds is not available. However, it was possible to position substernal pacing leads in all clinical subjects with thresholds that were substantially lower than the maximum output of commercially available temporary pacemakers.

Potential Clinical Use as a Temporary Pacing System

Currently available devices for temporary transvenous pacing expose patients to a high risk of complications besides restricting patients in their mobility.[6-8] With the increasing number of procedures, such as TAVR requiring temporary pacing for a certain time in frail patients, the limitations of current temporary pacing leads has become increasingly visible in clinics around the world.[9] Temporary transvenous pacing is associated with specific problems including lead instability, infection, hemorrhage, pneumothorax, patient discomfort and complication rates have not changed over time.[6-8] A reasonable interpretation of the persisting high complication rates is that the concept of temporary transvenous pacing has not changed considerably since its introduction. The current guidelines acknowledge the risks associated with temporary transvenous pacing and stress that it should be applied as briefly as possible.[10] These findings underline the necessity for alternative treatments for patients requiring temporary pacing. New technologies, such as the AtaCor extracardiac pacing system, may provide an alternative for patients who require temporary bradycardia pacing. We demonstrated here that placement of substernal pacing leads was feasible did not result in iatrogenic complications, such as damage to lung, pericardium, heart, internal thoracic vessels or other anatomic structures in these patients. Given that the current pacing thresholds are higher than in general accepted permanent pacing, this extracardiac pacing system currently seems a viable option for temporary pacing. The high thresholds currently limit the routine use of this pacing system as an alternative for permanent pacing. However, permanent pacing may also be achieved if lead optimization efforts in future developments would be able to reduce these pacing thresholds. High pacing thresholds were accepted at the onset of new therapies such as left ventricular pacing in the past as the trade-off for the potential benefit may be valuable, in the correct patient population. This may be the case for the AtaCor permanent pacing option as well. In some patients, we may accept shorter battery longevity in order to provide pacing without entering the vasculature.

Extracardiac Pacing Modalities Currently in Development

To avoid well-known complications of conventional PM and ICD therapy, new extravascular device approaches are in development. Jordan *et al.* fixated standard transvenous pacing leads to the left ventricular free wall and atrial appendage using the pericardial space in 5 piglets.[14] This approach, which was performed under thoracoscopic guidance, was feasible, yet one piglet developed a pneumothorax. John *et al.* successfully placed an intrapericardial lead percutaneously by a sub-xiphoid approach in a canine model.[15] Clark *et al*. demonstrated a single-incision ICD lead placement to the ventricular epicardial surface in 6 piglets without complications.[16] Bar-Cohen *et al.* presented a pericardial micro-pacemaker which was successfully implanted in 3 out of 6 pigs.[17] In addition, the SPACE study evaluated the feasibility of pacing in the substernal anterior mediastinum by using an electrophysiology catheter placed under fluoroscopy by using a malleable stainless

steel tunneling tool via a sub-xiphoid approach. Ventricular pacing was successful in 18 out of the 26 included patients.[18] There were 2 procedure-related adverse events. One patient suffered from incision-site pain, and one patient had pericardial effusion caused by the tunneling procedure. The feasibility study presented here describes a different minimally invasive approach of extracardiac pacing in the anterior mediastinum through the ICS using an easy to use custom delivery tool without the need for fluoroscopy, and without peri-procedural complications.

What's Next

Temporary pacing is a logical initial clinical indication for this novel technology as it can leverage commercially available temporary pulse generators and is limited to in-hospital use where medical oversight exists. Preliminary work supports that this extracardiac pacing lead technology will be deployable quicker than currently available transvenous temporary pacing leads, without requiring fluoroscopy and without the risks of vascular or intracardiac placement. Additionally, the potential for increased in-hospital ambulation without the risk of dislodgement also exists and must be studied. It is expected that pacing thresholds with an extracardiac pacing lead will be greater than what is required for endocardial pacing, but this is a non-issue for externally powered temporary generators. Subacute (up to 7 days) clinical data with final lead and delivery tool devices must be generated to demonstrate safety and effectiveness for temporary pacing indications.

Additional development efforts will then be required to address permanent pacing indications. Chronic lead optimization efforts to lower pacing thresholds and novel pulse generator designs that can accommodate higher capacity batteries will help to provide adequate longevity for permanent extracardiac pacing applications, despite higher thresholds. Ultimately, an alternative permanent pacemaker option with a reduction in longevity may still be an attractive option for some if the risks associated with intravascular or endocardial device placement can be eliminated. The development of chronic clinical data will also be required to ensure that this completely extracardiac pacing approach is safe and effective for permanent pacing.

Limitations

The current study has some limitations. The number of included human patients and cadavers is limited. The CT images in the anatomy study were retrospectively assessed. Two standard transvenous PM-leads, placed into the desired tissue location, were used for the evaluation of cardiac pacing performance (pacing tip-to-tip), and were not optimized for substernal pacing. Future human studies are required to evaluate the safety and efficacy of the AtaCor extracardiac pacing system for temporary and permanent PM therapy in different patient groups.

Conclusion

We report the feasibility of an innovative extracardiac pacing system with leads placed through an ICS that eliminates the need to place any hardware within the vasculature, pericardium or heart. This novel pacing approach showed to be anatomically feasible in a large heterogeneous patient population, using a minimally invasive delivery approach capable of ventricular sensing and pacing capture. The AtaCor extracardiac pacing system has the potential to provide clinically advantageous alternatives for patients requiring temporary.

Disclosures

Quast, Beurskens and Vehmeijer do not report any disclosures. Ebner has received research grants from AtaCor. Wasley received consultancy fees from AtaCor. Marcovecchio and Sanghera are employed by AtaCor and report equity in AtaCor. Knops reports consultancy fees, speaker fees and research grants from Boston Scientific, Abbott and Medtronic. Burke received speaking honoraria, research grants from Boston Scientific as well as Biosense Webster and consults for Abbott, Boston Scientific and AtaCor. Burke has equity in AtaCor.

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CHAPTER

9A

Thesis summary

Advances in Cardiac Pacemaker Systems:
Leadless and Extracardiac Pacing

Summary

This thesis begins in **chapter 2a** with a case that illustrates an example in which implantation of a tranvenous pacemaker was not possible and implantation of an epicardial pacemaker system was avoided by implanting a leadless pacemaker. The case describes a patient with a bilateral venous thoracic outlet syndrome. Hence, the physician was unable to implant the transvenous leads through the subclavian vein and the procedure was aborted. The leadless pacemaker was then successfully implanted as an alternative, since this device is placed into the right ventricle through the femoral vein. In **chapter 2b** describes a comprehensive overview of the leadless pacemaker technology including its indication, outcome, challenges, and continuing development.

Infection of the transvenous pacing system is considered one of the most serious complications, are potentially fatal, and in most cases require complete pacemaker system removal.(1-3) Patients that have an active infection during removal and implantation of a new transvenous device are more likely to develop a reinfection.(4-6) Therefore it is recommended to treat and active infection before implanting a new conventional pacing system. Yet, pacemaker dependent patients require a temporary pacing lead as a bridge to permanent transvenous pacemaker implantation. These temporary leads are very uncomfortable for patients and are associated with high complication rates.(7) In **chapter 3** a new idea was coined to implant a leadless pacemaker early after explantation of the infected transvenous pacemaker and proved to safe and effective. No reinfection of the leadless pacemaker was observed during the follow-up period.

Patients with bradyarrhythmia may suffer from serious invalidating symptoms such as dizziness, dyspnoe, lack of energy and syncope. By implanting a pacemaker the heart rate can be restored and thus the severity of symptoms can decrease. Health Related Quality of Life assessment is a way to measure the effectiveness of a therapy, such as after leadless pacemaker implantation, by determining the quality of life and clinical status of the patient. (8) In **chapter 4** it was concluded that the implantation of a Micra Transcatheter Pacing System resulted in an improvement of health-related quality of life, patient satisfaction and patient activity 3 and 12 month after implantation of the device.

Often when a new technique is introduced, there is a chance that more complications may occur during the initial implantations. This phenomenon is called the learning curve. In **chapter 5**, a learning curve analysis was performed of the Nanostim leadless pacemaker. It was concluded that serious adverse events occurred more often during the first 10 Nanostim implantations of the implanting physician. In addition, procedure time improved and the need for repositioning of the intracardiac device decreased with increasing implanting experience.

In **chapter 6a** and **6b** of this thesis one of the major challenges of leadless pacemaker is being discussed: its end-of-life management. The implanting physician can implant an additional leadless pacemaker next to the end-of-life leadless pacemaker without removing the non-functioning device. Or, an attempt can be made to extract the non-functioning leadless pacemaker and then place a new device into the right ventricle. Both strategies are being reviewed in this chapter. In addition, an illustrative case is described in detail.

Transvenous single-chamber pacing therapy can result in the development or intensification of tricuspid valve regurgitation.(9,10) Iatrogenic damage during lead implantation to the valve and/ or the continuing mechanical impact of the lead on the valves and/ or dyssynchronous right ventricular pacing may result in the development or increase of tricuspid valve regurgitation. By implanting a leadless pacemaker there might be no long-term mechanical impact on the tricuspid valves since there is no lead placed across the tricuspid valves. Yet, in **chapter 7** it was shown that leadless pacemaker therapy also resulted in an increase of tricuspid valve regurgitation. This may be caused by iatrogenic damage during leadless pacemaker implant and/ or mechanical impact and/ on the tricuspid subvalvular apparatus or right ventricular dyssynchronous pacing or other factors. This needs to be further investigated.

In **Chapter 8**, three feasibility studies are described involving a new pacing system that does not require transvenous leads. The new pacing system is a minimally invasive extracardiac temporary pacing system. A CT study was performed to evaluate through which intercostal spaces the anterior mediastinum could be reached. It was feasible to place a lead in the anterior mediastinum by using a custom made delivery tool through the 4^{th}, 5^{th}, or 6^{th} intercostal space with adequate pacing performance. Yet, the system requires further development and additional feasibility, non-clinical and clinical studies before it can be used in clinical practice.

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CHAPTER

9B

General Discussion

Advances in Cardiac Pacemaker Systems:
Leadless and Extracardiac Pacing

General Discussion

Since the first implantation of a transvenous pacemaker decades ago, the field of pacing therapy has been subject to on-going developments. (1) Transvenous pacing is widely used and considered safe and effective, yet investigators are continuously working on new pacing modalities to avoid complications associated with conventional pacemakers. Among others, his bundle branch pacing, left bundle branch pacing and leadless pacing have the potential to enhance outcome in specific patient groups that require long-term pacemaker therapy. His bundle and left bundle brand pacing provide a more physiological ventricular electrical activation compared to non-physiological right ventricular pacing. Therefore it potentially reduces the prevalence of pacemaker-induced cardiomyopathy, atrial fibrillation or even death. (1-2) Studies show that His bundle pacing can be used in specific patients with high-grade atrioventricular block, and decrease the QRS duration in some cases of right or left bundle branch block. (3-6) Yet, there are some limitations to his bundle pacing such as the difficult implant technique and high capture thresholds are not rare during follow-up. The other emerging conduction system pacing modality that may become an alternative to his bundle pacing, is left bundle branch pacing. The first clinical studies show that implantation of the device is safe and feasible. (7-10) Low pacing thresholds and left ventricular electrical synchrony were observed following left bundle branch pacing. A potential limitation of left bundle branch pacing is its end-of-life management and long-term performance of the lead. (1) In addition, similar to the conventional transvenous pacemaker, a pacemaker pocket is required. Therefore, complications related to pacemaker leads or pockets are potentially not circumvented. Although, several aspects of left bundle branch pacing are yet to explored, it may have the potential to play role a key role in the future in a subset of patients requiring pacing therapy. (11)

Leadless pacemaker therapy is a revolutionary innovation that has resulted in a new era of pacemaker therapy since lead and pocket-related adverse events no longer occur. The Nanostim leadless pacemaker and the Micra Transcatheter Pacing System have shown to be effective with a promising short- and intermediate-term safety outcome. Widespread use of leadless pacemakers instead of transvenous pacemakers, however, is currently limited. Recent developments in the field of leadless pacemakers focus on making this therapy available to all patients in need of a pacemaker. For years, the indication area has been confined to VVI(R) pacing only, but recently the Micra AV was introduced which is capable of VDD(R) pacing by accelerometer-based atrial sensing with good AV-synchrony at rest. (12) To achieve DDD(R) pacing, an atrial leadless pacemaker is being developed capable of wireless communication with a ventricular leadless pacemaker. (13) The indication area is further confined to older patients, as the retrievability and maximum number of co-implanted leadless pacemakers is unknown. Self-rechargeable

leadless pacemakers would circumvent this limitation and are currently being developed and tested *in vitro*. (14-17) Besides antibradycardia pacing, leadless pacemakers may also be used for anti-tachycardia and cardiac resynchronization therapy pacing in the future. The EMPOWER LCP (Boston Scientific) is designed to communicate wirelessly with a subcutaneous ICD and preclinical studies generated promising results. (18-19) Leadless cardiac resynchronization therapy pacing consists of a transvenous pacemaker or ICD in conjunction with a wireless endocardial pacing electrode in the left ventricle and its feasibility is demonstrated clinically. (20)

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CHAPTER

10

Nederlandse samenvatting

Ontwikkeling van pacemakers:
Draadloze en Extracardiale Pacemaker Systemen

Nederlandse samenvatting

Dit proefschrift begint in **hoofdstuk 2a** met een casus waarbij implantatie van een transveneuze pacemaker niet mogelijk was en een draadloze pacemaker werd geïmplanteerd als alternatief. Hiermee werd voorkomen dat een epicardiaal pacemaker systeem geïmplanteerd moest worden. De patiënt leed aan een bilateraal veneus thoracic outlet-syndroom en om deze reden kon de implanteur niet de transveneuze pacemakerdraden via de reguliere veneuze toegang implanteren vanwege obstructie. De procedure werd afgebroken. Als alternatief werd vervolgens de draadloze pacemaker geïmplanteerd, die via een andere route (vene femoralis) in de rechter hartkamer wordt geplaatst. In **hoofdstuk 2b** wordt een uitgebreid overzicht gegeven van de beschikbare data van de draadloze pacemaker, waaronder indicaties, klinische uitkomsten, uitdagingen en toekomstperspectieven.

Een infectie van het transveneuze pacemakersysteem wordt beschouwd als een van de meest ernstige complicaties. Een pacemakerinfectie kan een dodelijk gevolg hebben en vereist in de meeste gevallen volledige verwijdering van het pacemakersysteem. De kans op een re-infectie is groot als er nog een actieve pacemakerinfectie is ten tijde van de verwijdering van het geïnfecteerde systeem en plaatsing van een nieuwe pacemaker. Om deze reden wordt aangeraden om een actieve infectie eerst te behandelen voordat een nieuw pacemakersysteem geïmplanteerd kan worden. Dit is echter lastig voor patiënten die pacemakerafhankelijk zijn. Deze patiënten hebben namelijk ter overbrugging tot plaatsing van het nieuwe permanent systeem een tijdelijke pacemaker nodig. Deze tijdelijke pacemakers zijn zeer oncomfortabel voor patiënten en zijn geassocieerd met hoge complicatiecijfers. In **hoofdstuk 3** wordt een nieuwe strategie beschreven waarin een draadloze pacemaker wordt geïmplanteerd vroeg nadat het geïnfecteerde transveneuze pacemaker verwijderd was. Deze procedure bleek veilig en effectief te zijn. Er werd geen re-infectie van de draadloze pacemaker waargenomen tijdens de follow-up periode.

Patiënten met een te traag hartritme kunnen last hebben van duizeligheid, dyspneu, gebrek aan energie en syncope. Door implantatie van een pacemaker wordt de hartfrequentie hersteld, waardoor de ernst van deze symptomen afnemen. De gezondheid-gerelateerde kwaliteit van leven meting is een manier om de effectiviteit van een bepaalde therapie te meten. Dit wordt vaak gedaan bij nieuwe therapieën en zo ook voor de draadloze pacemaker therapie. In **hoofdstuk 4** wordt geconcludeerd dat de implantatie van een Micra Transkatheter Pacemaker Systeem resulteert in een verbetering van de gezondheid-gerelateerde kwaliteit van leven op 3 en 12 maanden na de implantatie. Daarbij werd de tevredenheid van de patiënten getoetst middels een vragenlijst voor implantatie, 3 en 12 maanden na implantatie. Er werd een evidente verbetering in de patiënt-tevredenheid

waargenomen. Ten slotte resulteerde implantatie van de draadloze pacemaker in een toename van activiteit bij de patiënten op zowel 3 als 12 maanden na implantatie.

Bij de initiële implantaties van een nieuwe techniek treden er vaak meer complicaties op. Zodra de ervaring van de implanteur toeneemt, wordt het vaak duidelijk dat de complicatie percentages afnemen. Dit verschijnsel wordt de leercurve genoemd. In **hoofdstuk 5** wordt een leercurve-analyse uitgevoerd van de implantatie van de Nanostim draadloze pacemaker. De conclusie is dat ernstige complicaties vaker optreden tijdens de eerste 10 Nanostim implantaties van de implanteur. Bij meer dan 10 implantaties werden minder complicaties waargenomen. Bovendien nam de proceduretijd af en nam de noodzaak van herpositionering van de draadloze pacemaker af naarmate de ervaring toenam.

In **hoofdstuk 6a en 6b** van dit proefschrift wordt een van de belangrijkste uitdagingen van de draadloze pacemaker behandeld: de meest optimale "end-of-life" strategie. Er zijn twee opties: de implanteur kan een nieuwe draadloze pacemaker naast de uitgevallen draadloze pacemaker plaatsen, zonder de niet-functionerende draadloze pacemaker te verwijderen. De tweede optie is dat de implanteur eerst de niet-functionerende draadloze pacemaker probeert te verwijderen en vervolgens een nieuwe draadloze pacemaker in de rechterventrikel plaatst. Beide strategieën worden in dit hoofdstuk besproken. Bovendien wordt een illustratieve casus in detail beschreven.

Transveneuze eenkamer pacemakers kunnen ontwikkeling of verergering van tricuspidalisklep regurgitatie veroorzaken. Dit kan verschillende oorzaken hebben zoals beschadiging van de klep tijdens de implantatie, en/of de voortdurende mechanische impact van de pacemakerdraad op de kleppen, en/of dyssynchronie van de kamers door rechterkamer pacing. Bij implantatie van een draadloze pacemaker is er geen pacemakerdraad die door tricuspidalisklep loopt, omdat de pacemaker volledig in de rechterkamer zit. De hypothese is dat er dan mogelijk minder tricuspidalisklep regurgitatie ontstaat omdat de mechanische impact op de klep sterk verminderd kan zijn. In **hoofdstuk 7** wordt echter aangetoond dat ook draadloze pacemaker therapie resulteert in een toename van de regurgitatie van de tricuspidalisklep. Dit kan mogelijk veroorzaakt worden door iatrogene schade tijdens de implantatie van de draadloze pacemaker, en/of mechanische impact op de subvalvulaire structuren van de tricuspidalisklep, en/of kamerdyssynchronie door rechterkamerpacing. Dit moet verder worden onderzocht.

In **hoofdstuk 8** worden drie haalbaarheidsstudies beschreven met betrekking tot een nieuw pacemakersysteem waarbij geen transveneuze pacemakerdraden nodig zijn. Het nieuwe pacemakersysteem is een minimaal invasief extracardiaal geplaatst tijdelijk pacemakersysteem. Er werd een CT-onderzoek uitgevoerd om te beoordelen via welke intercostale ruimten het anterior mediastinum kon worden bereikt. Het bleek haalbaar

om met een speciaal gemaakt plaatsingsinstrument via de 4e, 5e of 6e intercostale ruimte een pacemakerdraad in het anterior mediastinum te plaatsen. Daarbij werden adequate pacemaker parameters bereikt. Er zijn aanvullende ontwikkelingen nodig en additionele studies voordat het systeem in de klinische praktijk kan worden gebruikt.

APPENDICES

PhD portfolio
List of publications
Contributing authors
About the author - Curriculum Vitae
Dankwoord

PhD portfolio

Name PhD student:	Niek Beurskens
PhD period:	March 2017 – May 2020
Name PhD supervisor:	prof. dr. A.A.M. Wilde
Name PhD co-supervisor:	dr. R.E. Knops

1. PhD training	
	Year
General courses	
• Good Clinical Practise	2017
• CRT course, Abbott, Brussels	2018
• Medtronic Academia CIED training	2018
• Project Management	2019
Poster Presentations	
• Heart Rhythm Society scientific sessions	2018
• American Heart Association scientific sessions	2018
• European Heart Rhythm Association congress	2018
Oral Presentations	
• Heart Rhythm Society scientific sessions	2019, 2020
• American Heart Association scientific sessions	2019
• European Society of Cardiology congress	2018, 2019
• Asian Pacific Hearth Rhythm Society	2019
• European Heart Rhythm Association congress	2019
• Nederlandse Vereniging Voor Cardiologie congress	2019
• World Congress of Pediatric Cardiology and Cardiac Surgery	2017
(Inter)national conferences	
• Heart Rhythm Society scientific sessions	2018, 2019, 2020
• American Heart Association scientific sessions	2018, 2019
• European Society of Cardiology congress	2018, 2019
• Asian Pacific Hearth Rhythm Society	2019
• European Heart Rhythm Association congress	2018, 2019
• Nederlandse Vereniging Voor Cardiologie congress	2019
• World Congress of Pediatric Cardiology and Cardiac Surgery	2017

2. Teaching

	Year
Lecturing	
• Amstel Academy: ACS course for cardiac care nurses	2018, 2019
• Master Critical Care: Pacemaker Therapy	2018, 2019
• Master Critical Care: Medication	2018, 2019
• Abbott, leadless pacemaker developments	2019
• Abbott, ICD developments	2019
Supervising	
• Master thesis, daily supervisor of:	
1. Kosse Dasselaar	2017
2. Jilles van Drooge	2018
3. Chris Meijer	2019
4. Annelot Peijser	2019

3. Parameters of Esteem

	Year
Grants	
• KNAW Van Walree Beurs	2016
• Holland Scholarship Programme	2016
• Marco Polo Fonds	2016
• Hendrik Muller's Vaderlandsch Fonds	2016
• Stichting de Fundatie van de Vrijvrouwe van Renswoude	2016
• J.C. de Cock stichting	2016
• Groningeruniversiteitsfonds (GUF)	2016
• UMCG subsidie	2016
• Stichting de Drie Lichten	2020
• Reisbeurs promovendi UvA	2020
• Spinoza Fonds – Amsterdam Universiteitsfonds	2020

4. Publications

	Year
Peer reviewed	
• See list of publications	
Manuscripts reviewed for	
• JACC – EP	2018
• Circulation – Arrhythmia and Electrophysiology	2019
• Heart Rhythm Journal	2019

List of Publications

1. **Niek E.G. Beurskens**, Fleur V.Y. Tjong, Kosse J. Dasselaar, Wichert J. Kuijt, Arthur A.M. Wilde, Reinoud E. Knops Leadless pacemaker implantation after explantation of infected conventional pacemaker systems: A viable solution? Heart Rhythm. 2019 Jan;16(1):66-71

2. **Beurskens NEG**, Tjong FVY, de Bruin-Bon RHA, Dasselaar KJ, Kuijt WJ, Wilde AAM, Knops RE.
   Impact of Leadless Pacemaker Therapy on Cardiac and Atrioventricular Valve Function Through 12 Months of Follow-Up. Circ Arrhythm Electrophysiol. 2019 May;12(5):e007124

3. **Beurskens NEG**, Hagdorn QAJ, Gorter TM, Berger RMF, Vermeulen KM, van Melle JP, Ebels TE, Lui GK, Ceresnak SR, Chan FP, Willems TP. Risk of cardiac tachyarrhythmia in patients with repaired tetralogy of Fallot: a multicenter cardiac MRI based study. Int J Cardiovasc Imaging. 2019 Jan;35(1):143-151

4. **Niek E.G. Beurskens***, Karel T.N. Breeman*, Kosse J. Dasselaar, A. Chris Meijer, Anne-Floor B.E. Quast, Fleur V.Y. Tjong, Reinoud E. Knops. Leadless cardiac pacing systems: current status and future prospects. Expert Rev Med Devices. 2019 Oct 28
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5. **Niek E. G. Beurskens***, Anne-Floor B. E. Quast*, Richard Wasley, Jim T. Vehmeijer, Alan Marcovecchio, Rick Sanghera, R.E. Knops, Martin Burke. Feasibility of an Entirely Extracardiac, Minimally Invasive, Temporary Pacing System. Circ Arrhythm Electrophysiol.. 2019 Jul;12(7)
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6. **Niek E.G. Beurskens***, Fleur V.Y. Tjong*, Joris R. de Groot, Catherine Waweru, Shufeng Liu, Philippe Ritter, Dwight Reynolds, Arthur A.M. Wilde, MD, and Reinoud E. Knops MD, for the Micra Investigators. Health-Related Quality of Life Impact of a Transcatheter Pacing System. J Cardiovasc Electrophysiol. 2018 Dec;29(12):1697-1704
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8. **Beurskens NE**, Tjong FV, Knops RE, Peters RJ. Percutaneous leadless pacemaker implantation in a patient with bilateral venous thoracic outlet syndrome. J Vasc Access. 2019 Jan;20(1):105-106

9. **Beurskens NEG**, Tjong FVY, Quast ABE, Knops RE. Successful replacement of the longest worldwide in situ Nanostim leadless cardiac pacemaker for a Micra Transcatheter Pacing System. J Interv Card Electrophysiol. 2018 Mar;51(2):161-162

10. Hagdorn QAJ, **Beurskens NEG**, Gorter TM, Eshuis G, Hillege HL, Lui GK, Ceresnak SR, Chan FP, van Melle JP, Berger RMF, Willems TP. Sex differences in patients with repaired tetralogy of Fallot support a tailored approach for males and females: a cardiac magnetic resonance study. Int J Cardiovasc Imaging. 2020 Oct;36(10)

11. **Beurskens NE**, Tjong FV, Knops RE. End-of-life Management of Leadless Cardiac Pacemaker Therapy. Arrhythm Electrophysiol Rev. 2017 Aug;6(3):129-133

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CMR feature tracking left ventricular strain-rate predicts ventricular tachyarrhythmia, but not deterioration of ventricular function in patients with repaired tetralogy of Fallot. Int J Cardiol. 2019 Aug 1

14. Tjong FVY, de Ruijter UW, **Beurskens NEG**, Knops RE. A Comprehensive Scoping Review on Transvenous Temporary Pacing Therapy. Neth Heart J. 2019 Aug 7

15. Karel T N Breeman, Romy du Long, **Niek E G Beurskens**, Allard C van der Wal, Arthur A M Wilde, Fleur V Y Tjong, Reinoud E Knops. Tissues attached to retrieved leadless pacemakers: histopathologic evaluation of tissue composition in relation to implantation time and complications. HeartRhythm. 2021 Aug 27;S1547-5271(21)02094-4.

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Curriculum Vitae

Niek Beurskens was born on the 30th of September 1990 in Tegelen (the Netherlands) to Twan Beurskens and Angelique Beurskens-Witteveen. Niek has 2 older brothers named Twan Beurskens Jr., and Thijs Beurskens. Niek followed the International Baccalaureate program at Den Hulster high school from 2002 to 2008 and included internships in Cambridge, Galway and Germany. Niek started medical school at the University of Groningen in 2009. He worked at the emergency general practitioner post. In addition, Niek was a member of the organization of the International Student Congress of (bio) Medical Sciences. After residencies in Zwolle and Uganda and a research period at Stanford University in Palo Alto (USA), Niek completed his medical training at the University Medical Center Groningen in February 2017. In March 2017, Niek started his PhD trajectory in the Department of Cardiology (Electrophysiology) at the Amsterdam UMC – University of Amsterdam. His supervisors were dr. RE Knops, dr. FVY Tjong, and prof. dr. AAM Wilde. The topics of the PhD projects focused on novel pacing therapies. The publications resulting from the projects led to his thesis and resulted in multiple presentations held in the US, Europa and Asia. It was intended to complete the PhD program at the Icahn School of Medicine at Mount Sinai in New York. Niek started his research period there, yet returned to Amsterdam because of the Covid-19 pandemic. Despite the fact that Niek remains very interested in the scientific field of Cardiology, he decided to make a career switch. Niek started working as a doctor at the Mentrum Hospital for patients with severe psychiatric disorders in Amsterdam. Subsequently, he started his Psychiatry Residency Program at the Erasmus University Medical Center in Rotterdam.

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