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ORIGINAL ARTICLE

Leadless Permanent Pacing: A Single Centre Australian Experience

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Background To describe the performance and clinical outcomes of consecutive patients having a leadless pacemaker (LP) implanted at a single institution.

Methods Clinical data and device parameters were prospectively collected on all patients undergoing LP implantation from November 2015 to April 2018.

Results A total of 79 patients (52 male), median age of 78 years, was included. Leadless pacemaker implantation was successful in 76 patients (96%). Implantation failed in two patients due to excessive venous tortuosity and due to inadequate sensing in another. Seventy-three (73) patients (96%) had chronic atrial fibrillation and all had a Class I or II indication for pacing. Procedure time was 29 minutes (IQR 21–43) and fluoroscopy time was 8 minutes (IQR 5–13). The median R wave at implant was 11.2 mV (IQR 6.9–15.0). The median capture threshold at 0.24 ms was 0.5 V (IQR 0.4–0.9) and impedance was 754 Ω (IQR 680–880). Intraprocedural acute dislodgement occurred in one patient following cutting of the tether but successful snaring and reimplantation was performed. During a median follow-up of 355 days (range 9–905), overall electrical performance has been excellent. No patients have been readmitted for device revision or complications. Five (5) patients (7%) died during follow-up from unrelated causes.

Conclusions Leadless pacemakers can be implanted safely and effectively in the majority of patients. Device electrical performance was excellent over a median follow-up of 12 months.

Keywords Bradycardia • Heart block • Leadless pacemaker • Atrial fibrillation

Introduction

Permanent pacing is an established treatment for patients with various bradyarrhythmias. Since the 1960s, it has been delivered via a surgically implanted pulse generator attached to one or more transvenously deployed intracardiac pacing electrodes. While effective, up to one in eight patients suffers complications [1–3]. These complications include pocket sepsis, haematomas and risks related to lead insertion including pneumothorax, haemothorax and pericardial effusion.

In the longer term, transvenous leads are associated with multiple complications including vascular occlusion, tricuspid valve dysfunction, intravascular lead-related infections and lead integrity issues related to subclavian crush, conductor fracture and insulation failure.

Advances in technology over the last decade have resulted in miniaturisation of pacemaker componentry to the point that an entirely intracardiac pacing system can now be implanted within the heart [4–7]. Initial reports suggest that such leadless pacemakers may have advantages over

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traditional transvenous devices with post-hoc analysis suggesting a 51% lower adverse event rate at 6 months [6].

This study reports the initial implant experience and short-term outcomes of patients with leadless pacing at a single Australian centre.

Methods

We prospectively collected clinical data and device parameters on consecutive patients undergoing leadless pacemaker (LP) implantation at The Prince Charles Hospital from November 2015 to April 2018.

Implant Procedure

The Micra (Medtronic Inc. Minneapolis, MN, USA) transcatheter pacemaker is a self-contained capsule with a volume of 0.8 cm^3, a length of 25.9 mm and outer diameter of 6.7 mm. It weighs 2.0 grams and has a passive intracardiac fixation mechanism consisting of four nitinol tines. It is a fully functional single chamber rate responsive (VVIR) permanent pacemaker. The device has automated pacing capture threshold management to maximise battery longevity. It has remote monitoring capabilities and is approved for up to 3.0 T magnetic resonance imaging (MRI) scans without restrictions. The projected battery longevity is approximately 12 years.

The device was implanted using a steerable catheter delivery system inserted via the femoral vein. The right femoral vein was accessed using a modified Seldinger technique. An 8F sheath was inserted and a venogram of the femoral/iliac vein performed. If the vein was of a suitable size (i.e. greater than 10 mm in minimal diameter and with no significant tortuosity) a 180 cm Amplatz Super stiff 0.035" 3 mm J-tip guidewire (Boston Scientific Corp, Marlborough, MA, USA) was then advanced under fluoroscopic guidance to the superior vena cava. If difficulties were encountered advancing the super stiff wire, a standard 145 cm 0.035" J-tip guidewire was advanced to the superior vena cava, then exchanged through a 6F multipurpose catheter. The venous access was then progressively dilated with 12, 18 and 22F dilators (Cook Medical Inc., Bloomington, IN, USA) followed by insertion of an introducer sheath with lubricious hydrophilic coating (27F outer, 23F inner diameters) which was advanced to the low right atrium/inferior vena cava junction. This was continuously flushed with heparinised normal saline. The right ventricular apical septal region was the target implant site. However, when this region was found to have inadequate pacing and/or sensing threshold, a site in the mid to high right ventricular septum was chosen.

Prior to deployment of the LP, ventriculography was performed using the delivery catheter in two orthogonal views. This ensured that the pacemaker was implanted on the septal wall of the right ventricle avoiding the free wall which is associated with a higher rate of cardiac perforation [5]. The LP was then deployed with firm forward pressure. After release of the pacemaker from the delivery sheath, adequate attachment was confirmed with a "tug test" using cineradiography at 30 frames/second. Satisfactory initial placement required visual confirmation of attachment of at least two of the four nitinol tines.

Electrical performance was then tested targeting a threshold of less than 1.0 V at 0.24 ms and an R wave of greater than 5.0 mV. If, after approximately 5 minutes of observation, adequate electrical values was not obtained, the pacemaker was re-captured and an alternative right ventricular location chosen. If, after 10 attempts at repositioning, an adequate site was not obtained, the procedure was abandoned and a standard transvenous system implanted.

After obtaining a suitable site with acceptable electrical performance the LP was then released by cutting the tether. The sheath was removed and haemostasis obtained with a figure-of-8 femoral suture [8]. The suture was removed 6 hours post-procedure and the patient mobilised. All patients were admitted overnight for observation. The pacemaker was interrogated the following morning and the patients discharged if medically fit and device parameters remained acceptable.

Data Collection

Clinical data was collected prospectively including the indication for pacing, associated cardiac disease and medical comorbidities. Procedural outcomes and complications were recorded. Follow-up was scheduled for post-procedural day 1, 6 weeks, 3 months, 6 months and annually thereafter. All late complications related to the procedure were collected. This report was prepared after a minimum of 30 patients had been followed for at least 6 months post implant.

The selection of patients for a LP was at the discretion of the implanting electrophysiologist. All patients had American Heart Association/Heart Rhythm Society (AHA/HRS) Class I/II indication [9] for permanent pacing. The study was approved by The Prince Charles Hospital Human Research Ethics Committee (HREC/17/QPCH/495)

Statistical Analysis

Continuous data is expressed as median and inter-quartile range. Statistical analysis was performed using the R statistical package Version 3.4.4 (www-r-project.org).

Results

From November 2015 to April 2017, a total of 79 patients underwent LP implantation. Baseline clinical characteristics are summarised in Table 1. The median age was 78 years (IQR 72–84) 52 of which were male (67%). Seventy-six (76) (96%) patients were in permanent atrial fibrillation (AF). The remaining three (4%) patients were in sinus rhythm. The median ejection fraction was 58% (IQR 53–64). There was a relative contraindication to a transvenous pacemaker in 16 patients. This included infection (nine patients), SVC obstruction (five patients), renal dialysis (two patients) and prior tricuspid valve surgery (six patients). Some patients had more than one contraindication.

Table 1 Baseline demographics of all 79 patients.

Patients offered leadless pacing (n = 79)	
Age (yrs (IQR))	78 (72–84)
Left ventricular ejection fraction (% (IQR))	58 (53–64)
Gender	n (%)
Male (%)	52 (66)
Female (%)	37 (34)
Rhythm at time of implant	
Permanent atrial fibrillation with slow VR or intermittent pauses	61 (77%)
Permanent atrial fibrillation with CHB	15 (19%)
Sinus rhythm with CHB	1 (1)
Sinus node dysfunction	2 (3)
Prior transvenous device	10 (13)
Relative contra indication for transvenous device	16 (20%)
Infection	9 (11%)
SVC obstruction	5 (6%)
Tricuspid valve surgery	6 (8%)
Renal dialysis	2 (3%)
Anticoagulation at time of implant	
Novel oral anticoagulants	35 (44%)
Warfarin	22 (28%)
Antiplatelets	
Aspirin	6 (8%)
Clopidogrel	3 (4%)
Dual anti platelets	3 (4%)

Abbreviations:VR, ventricular response; CHB, complete heart block; SVC, superior vena cava

The procedure was successful in 96% (76 patients). The implant was unsuccessful in three patients. This was as a result of excessive venous tortuosity in two patients and poor R wave sensing in one patient (despite multiple attempts at repositioning in the right ventricular apical septal region).

The procedure was performed under local anaesthetic in 75 (95%) patients, and general anaesthetic in four patients, all of whom were undergoing extraction of a previously implanted transvenous device and re-implantation of an LP during a single procedure.

Fifty-seven (57) (72%) patients were anti-coagulated at the time of the LP implantation. Twenty-two (22) patients were on warfarin with a median international normalised ratio (INR) of 2.2. The remaining patients were taking apixaban (15 patients), dabigatran (4 patients) or rivaroxaban (16 patients). Antiplatelet agents were used in 12 (15%) patients including aspirin (six patients), clopidogrel (three patients) and dual antiplatelet therapy (aspirin/clopidogrel–three patients). Leadless pacemaker implantation was performed on uninterrupted anticoagulant/antiplatelet therapy in all cases.

Procedural details are summarised in Table 2. Patients occupied the electrophysiology lab for a median of 65 minutes (IQR 54–84), the median procedure time was 29 minutes (IQR 21–43) and the device was deployed in a median of two attempts (range 1–7). The median fluoroscopy time was 8 minutes (IQR 5–13) and the median dose area product was 752 uGycm^2 (IQR 331–1233).

The median R wave at implant was 11.2 mV (IQR 6.9–15.0), the median impedance was 754 Ω (IQR 680–880) and the median threshold at 0.24 ms pulse width was 0.5 V (IQR 0.4–0.9). The pacemaker was implanted in the right ventricular

Table 2 Procedural details of 76 successful implants.

N = 76	Median (IQR)
Procedure time (mins)	29 (21–43)
Fluoroscopy time (mins)	8 (5–13)
Dose area product (uGycm^2)	752 (331–1233)
Location of Implant	
Right ventricular apical septum	69 (91%)
Right ventricular outflow tract	7 (9%)
Number of deployments	2 (1–3)
R wave (mV)	11.2 (6.9–15.0)
Threshold (V @ 0.24 ms)	0.5 V (0.4–0.9).
Impedance (Ω)	753.5 (680–880)

apical septum in 69 patients (87%) and in the right ventricular outflow tract in seven patients.

In one patient, the LP dislodged acutely following release of the tether and lodged in the left pulmonary artery. The device was successfully retrieved with the aid of a 30 mm Amplatz Goose Neck Snare (Medtronic Inc. Minneapolis, MN, USA) and a deflectable sheath. Two days later a LP was implanted successfully without complications.

An adverse event within 24 hours of implant occurred in two patients. One patient developed symptomatic ventricular tachycardia after obtaining venous access but prior to any instrumentation of the heart. A transvenous implantable cardioverter defibrillator (ICD) was not implanted as the patient had a previous left-sided ICD removed following a pocket infection and two subsequent attempts at right-sided re-implantation had failed due to the absence of a right superior vena cava. He was in permanent AF with a slow ventricular response. While occurring during the implant procedure, it was felt to be related to his underlying cardiac condition rather than the procedure. His clinical condition deteriorated over the next 9 days resulting in death from refractory cardiac failure. A second patient developed significant pleuritic chest pain post procedure. An echocardiogram showed no evidence of a pericardial effusion. He was discharged the following day with simple analgesia and his symptoms resolved spontaneously with no sequale.

Patients were discharged a median of one day (IQR 1–2) post-procedure. Delays beyond one day were related to associated medical conditions or transport issues, rather than the LP implantation procedure itself.

During a median follow-up of 355 days (range 9–905), device electrical performance has remained stable (Figure 1). At last follow-up all patients had thresholds of less than 1.2 V at 0.24 ms. All patients had adequate R waves and impedances have remained stable. Early battery performance has been excellent. No patient has been re-admitted for a device related complication or the need for system revision.

Five patients (6%) died during follow-up. The cause of death was related to malignancy in four patients and refractory cardiac failure in one patient. All deaths were felt to be unrelated to the LP implant.

Discussion

This study outlines the initial experience with leadless pacing in a single Australian centre. The main findings are:

1. Leadless pacemakers can be implanted effectively and rapidly in the majority of patients with acceptable fluoroscopy exposure.
2. The implant and follow-up complication rate is low in this series.
3. Electrical performance at short-term follow-up is excellent.

The LP potentially represents the dawn of a major technological disruption in the delivery of cardiac pacing. For the first time, the two largest liabilities of a single-chamber pacing system, namely the lead and the pocket are dispensed with and the entire system is contained within the right ventricle. In this study, we found that implantation was successful and uncomplicated in the majority of patients with favourable procedure times and acceptable radiation exposure. The learning curve was short and the procedure was rapidly incorporated into a busy electrophysiology laboratory workflow with minimal disruption and no additional infrastructure requirements. The procedure was successful in 96% of patients who were able to return to normal activity almost immediately without restriction. No major complications were observed. Importantly no device-related infections, complications or revisions have occurred and no patient has re-presented to hospital for a device-related problem.

Short-term electrical performance in these patients was excellent but clearly longer-term follow-up is necessary to evaluate chronic device performance. In transvenous pacing systems, by 12 months after implant, the electrode-myocardial interface has usually matured and it is relatively rare for late changes in electrical parameters to occur beyond this time. Given that the LP's electrode has been modelled closely on a previous transvenous electrode with excellent long-term performance, the risk of late capture threshold increase would appear to be low.

Ideally a randomised clinical trial (RCT) is needed to evaluate the advantages and disadvantages of LPs over transvenous pacemakers, however, this is clearly not feasible to perform at a single institution. The relatively low event rates with both leadless and transvenous pacemakers would require a multicentre study of several thousand patients over a very long follow-up period to detect clinically relevant differences. Even the use of propensity matching and attempts to retrospectively match controls may not fully account for selection biases. Our experience is consistent with prior published observational data [10] and an expensive, large RCT in patients evaluating single-chamber pacing may not be viable. As the technology evolves into dual-chamber devices, a RCT will be mandatory to evaluate the comparative efficacy, performance and safety of LP given the significantly increased complexity of such systems.

While the optimal site of right ventricular pacing is still not clear, recent observational studies suggest that His bundle pacing may have some advantages [11] Currently, LPs can only be deployed in the right ventricular apex or septum, and this may potentially limit uptake if His bundle pacing proves superior in RCTs. This is in addition to the obvious main present LP limitation of only providing single-chamber ventricular based pacing. Consequently, the device is of relevance only to the approximately 20% of patients with a pacing indication who currently receive a single-chamber pacemaker [12]. A preliminary algorithm utilising accelerometer based sensing of atrial contraction has been developed which may allow for sequential atrioventricular (AV) (VDI) pacing using the current single chamber LP hardware in the future [13]′ expanding the indication of this LP to

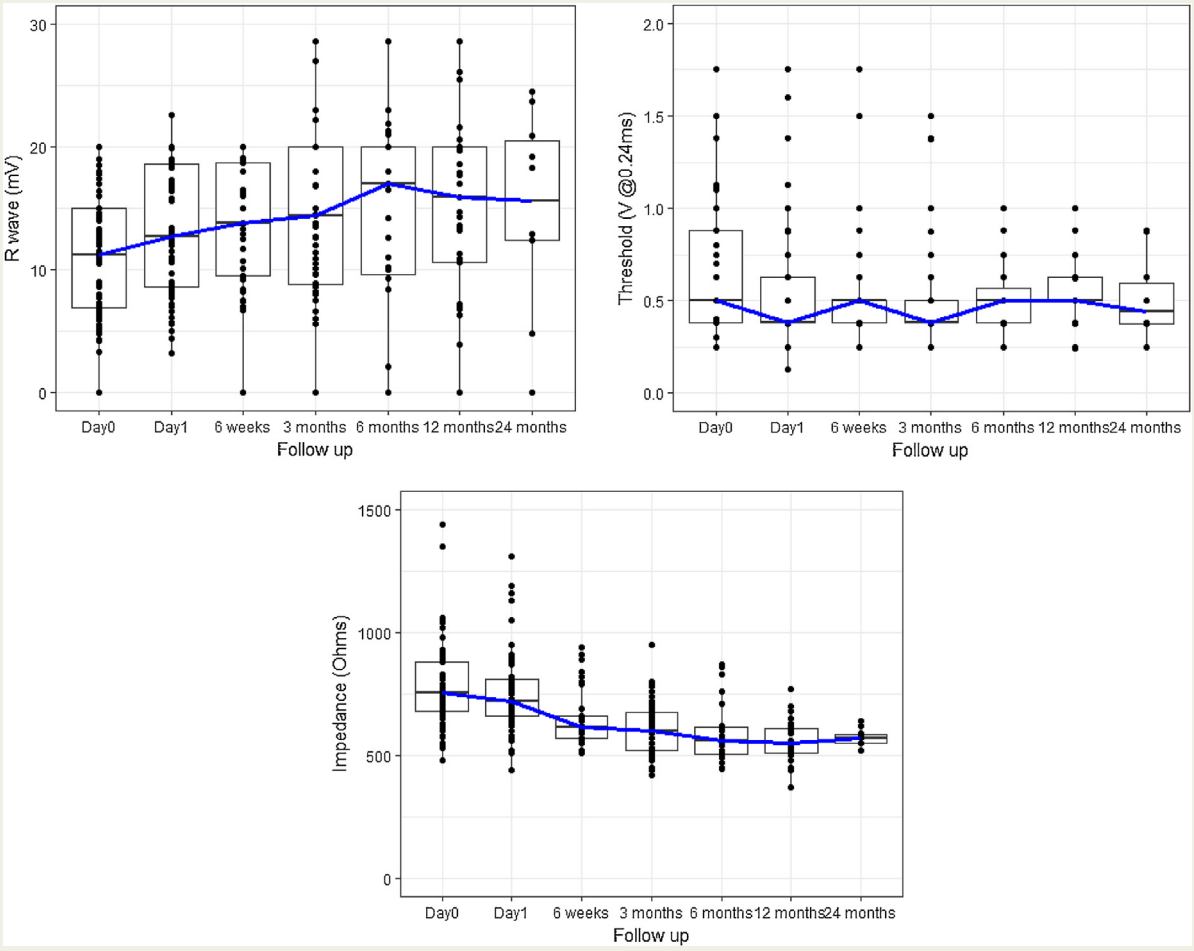

Figure 1 Electrical performance of the Micra Leadless Pacemaker (Medtronic Inc. Minneapolis, MN, USA) during follow-up.

patients with AV block. Further developments will be required to provide atrial and then dual-chamber pacing.

Leadless pacemakers are currently at least A$3,000 dollars more expensive than traditional single-chamber transvenous pacing systems. A full evaluation of the cost effectiveness was beyond the scope of this study, however, it is likely that the price will fall as other manufacturers enter the market. The full cost effectiveness of the devices requires looking at the cost over the lifetime of the patient. Late complications seen with traditional pacemakers, especially lead failure, pocket-related complications, tricuspid valve dysfunction and lead-related infections are avoided with leadless pacing. These complications are expensive to treat and their elimination may improve the overall cost effectiveness of LP.

Device management at the time of battery depletion is still an uncertain issue. The estimated longevity of the LP based on early performance is likely to be greater than 10 years. While early removal of the device has been described [14] it is likely that the majority of the devices will become fully endothelialised over time which will make removal percutaneously almost impossible. The device can be deactivated permanently and reports suggest at least three devices can be implanted in the right ventricle with no effect on cardiac performance [15]. Most patients with a single chamber pacing indication have permanent atrial fibrillation and are of an advanced age; it is likely that additional devices will be able to be implanted with no clinically significant adverse sequelae but this may not remain the case with the advent of dual chamber LP systems.

Limitations

The number of patient years of LP exposure in this study is relatively small and, therefore, the ability to detect rare complications is limited. A larger study with longer term follow-up would be required. A manufacturer sponsored registry is currently enrolling approximately 1,800 patients and is powered to detect complications with an incidence as low as 1% over the expected life of the device. The favourable early results of the first 795 patients have been recently published [16].

Conclusions

This report outlines the initial experience of 79 consecutive patients undergoing leadless pacemaker implantation at a

single Australian institution. The procedure was rapid, effective, well-tolerated and without major complications, consistent with prior published data. Device electrical performance over short-term follow-up was excellent. Larger studies with longer term follow-up are required to fully evaluate this promising new pacing technology.

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