Leadless Pacemakers

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Cardiac Electrophysiologist
Historical Background

1932 → 1st external cardiac pacemaker system by Alber S. Hyman

1958 → 1st complete epicardial pacing system by Rune Elmquist and Åke Senning

1968 → 1st transvenous temporary pacing lead the same year by Seymour Furman

### Reliable but ...

<table>
<thead>
<tr>
<th>Cumulative incidence of complications at six months(^a)</th>
<th>All ((n = 5918))</th>
<th>New implant ((n = 4355))</th>
<th>Generator replacement ((n = 1136))</th>
<th>Upgrade/lead revision ((n = 427))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any complication</td>
<td>562 (9.5; 8.7–10.2)</td>
<td>432 (9.9; 9.0–10.8)</td>
<td>67 (5.9; 4.5–7.3)</td>
<td>63 (14.8; 11.4–18.1)</td>
</tr>
<tr>
<td>Any major complication</td>
<td>329 (5.6; 5.0–6.1)</td>
<td>253 (5.8; 5.1–6.5)</td>
<td>40 (3.5; 2.4–4.6)</td>
<td>36 (8.4; 5.8–11.1)</td>
</tr>
<tr>
<td>Any minor complication</td>
<td>250 (4.2; 3.7–4.7)</td>
<td>189 (4.3; 3.7–4.9)</td>
<td>30 (2.6; 1.7–3.6)</td>
<td>31 (7.3; 4.8–9.7)</td>
</tr>
</tbody>
</table>

#### Major complications

- **Lead related re-intervention**: ✔
  - All: 143 (2.4; 2.0–2.8)
  - New implant: 120 (2.8; 2.3–3.2)
  - Generator replacement: 10 (0.9; 0.3–1.4)
  - Upgrade/lead revision: 13 (3.0; 1.4–4.7)

- **Infection**
  - All: 49 (0.8; 0.6–1.1)
  - New implant: 24 (0.6; 0.3–0.8)
  - Generator replacement: 17 (1.5; 0.8–2.2)
  - Upgrade/lead revision: 8 (1.9; 0.6–3.2)

- **Local infection**
  - All: 22 (0.4; 0.2–0.5)
  - New implant: 10 (0.2; 0.1–0.4)
  - Generator replacement: 8 (0.7; 0.2–1.1)
  - Upgrade/lead revision: 4 (1.0; 0.0–1.9)

- **Systemic infection/endocarditis**: ✔
  - All: 27 (0.5; 0.3–0.6)
  - New implant: 14 (0.3; 0.2–0.5)
  - Generator replacement: 9 (0.8; 0.3–1.3)
  - Upgrade/lead revision: 4 (0.9; 0.0–1.9)

- **Pneumothorax requiring drainage**
  - All: 51 (0.9; 0.6–1.1)
  - New implant: 45 (1.0; 0.7–1.3)
  - Generator replacement: 0
  - Upgrade/lead revision: 6 (1.4; 0.3–2.5)

- **Cardiac perforation**: ✔
  - All: 38 (0.6; 0.4–0.8)
  - New implant: 35 (0.8; 0.5–1.1)
  - Generator replacement: 0
  - Upgrade/lead revision: 3 (0.7; 0.0–1.5)

- **No intervention**
  - All: 21 (0.4; 0.2–0.5)
  - New implant: 18 (0.4; 0.2–0.6)
  - Generator replacement: 0
  - Upgrade/lead revision: 3 (0.7; 0.0–1.5)

- **Intervention\(^b\)**
  - All: 17 (0.3; 0.2–0.4)
  - New implant: 17 (0.4; 0.2–0.6)
  - Generator replacement: 0
  - Upgrade/lead revision: 0

- **Pocket revision because of pain**
  - All: 25 (0.4; 0.3–0.6)
  - New implant: 10 (0.2; 0.1–0.4)
  - Generator replacement: 9 (0.8; 0.3–1.3)
  - Upgrade/lead revision: 6 (1.4; 0.3–2.5)

- **Generator-lead interface problem with re-intervention**: ✔
  - All: 7 (0.1; 0.0–0.2)
  - New implant: 3 (0.1; 0.0–0.1)
  - Generator replacement: 4 (0.4; 0.0–0.7)
  - Upgrade/lead revision: 0

- **Haematoma requiring re-intervention**
  - All: 10 (0.2; 0.1–0.3)
  - New implant: 9 (0.2; 0.1–0.3)
  - Generator replacement: 1 (0.1; 0.0–0.3)
  - Upgrade/lead revision: 0

- **Other\(^c\)**
  - All: 16 (0.3; 0.1–0.4)
  - New implant: 16 (0.4; 0.2–0.5)
  - Generator replacement: 0
  - Upgrade/lead revision: 0

#### Minor complications

- **Haematoma\(^d\)**
  - All: 138 (2.3; 1.9–2.7)
  - New implant: 104 (2.4; 1.9–2.8)
  - Generator replacement: 20 (1.8; 1.0–2.5)
  - Upgrade/lead revision: 14 (3.3; 1.6–5.0)

- **Wound infection treated with antibiotics**
  - All: 69 (1.2; 0.9–1.4)
  - New implant: 47 (1.1; 0.8–1.4)
  - Generator replacement: 12 (1.0; 0.5–1.7)
  - Upgrade/lead revision: 10 (2.3; 0.9–3.8)

- **Pneumothorax conservatively treated**
  - All: 39 (0.7; 0.5–0.9)
  - New implant: 32 (0.7; 0.5–1.0)
  - Generator replacement: 0
  - Upgrade/lead revision: 7 (1.6; 0.4–2.8)

- **Lead dislodgement without re-intervention**
  - All: 10 (0.2; 0.1–0.3)
  - New implant: 9 (0.2; 0.1–0.3)
  - Generator replacement: 0
  - Upgrade/lead revision: 1 (0.2; 0.0–0.7)

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## RV lead causing Tricuspid Regurgitation

<table>
<thead>
<tr>
<th>Studies</th>
<th>Year</th>
<th>Number of pts</th>
<th>Study design</th>
<th>Type of device</th>
<th>Findings</th>
<th>Study limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sakai et al.</td>
<td>1987</td>
<td>18 pts</td>
<td>Prospective</td>
<td>PPM</td>
<td>• 5 pts (28%) had TR</td>
<td>• Small sample</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26 path reports from autopsies</td>
<td></td>
<td></td>
<td>• 11 autopsies (42%)→interference of valve motion by pacer leads</td>
<td>• Time course for TR development and progression after device implantation is not fully defined</td>
</tr>
<tr>
<td>Paniagua et al.</td>
<td>1998</td>
<td>374</td>
<td>Retrospective</td>
<td>PPM</td>
<td>• There was &gt; moderate TR in 7.2% cases vs 1.7% in controls (P&lt;.0001)</td>
<td>• Single-center experience</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Case-control</td>
<td></td>
<td>• Pts with PPM leads have an ↑ prevalence of significant TR</td>
<td></td>
</tr>
<tr>
<td>Leibowitz et al.</td>
<td>2000</td>
<td>35</td>
<td>Prospective</td>
<td>PPM</td>
<td>• More than moderate TR in 10 patients before and 7 patients after PPM implantation (P=NS)</td>
<td>• Small sample</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• PPM implantation is not usually associated with an acute worsening of TR</td>
<td>• Single-center experience</td>
</tr>
<tr>
<td>Lin et al.</td>
<td>2005</td>
<td>41</td>
<td>Retrospective</td>
<td>PPM/ICD</td>
<td>• Damage to the tricuspid valve by PPM or ICD leads may result in severe symptomatic TR and may not be overtly visualized by TTE</td>
<td>• Retrospective methodology</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 41 patients referred for TV surgery because of severe TR due to endocardial lead</td>
<td>• Single-center experience</td>
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<td></td>
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<td></td>
<td>• Pts with other heart conditions such as LV dysfunction, pulmonary hypertension were not excluded and these could have contributed to the worsening in severity of TR</td>
</tr>
<tr>
<td>Kucukarslan et al.</td>
<td>2006</td>
<td>61</td>
<td>Prospective</td>
<td>PPM</td>
<td>• After implantation, TR severity was increased from normal/trivial to mild in 5 (16%) cases and from mild to moderate in 3 (10%)</td>
<td>• Single-center experience</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• There was no worsening of the severity of TR in patients with moderate regurgitation following device implantation</td>
<td>• Small sample</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• The severity of TR did not change at a mean follow-up of 6±3 months</td>
<td>• Shadowing of the PPM lead might cause an underestimation of the severity of the TR</td>
</tr>
<tr>
<td>Webster et al.</td>
<td>2008</td>
<td>123</td>
<td>Retrospective</td>
<td>ICD</td>
<td>In patients with transvenous ventricular leads across the TV, TTE demonstrates a small, but statistically significant change in TR</td>
<td>• Retrospective methodology</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Single-center experience</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>2008</td>
<td>248</td>
<td>Retrospective</td>
<td>PPM/ICD</td>
<td>• After implantation, abnormal TR developed in 21.2% and severe TR developed in 3.9% of pts with initially normal TR. TR worsened by at least 1 grade in 24.2%</td>
<td>• Retrospective methodology</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Patients with ICDs had a higher rate of TR worsening compared with patients with PPMs</td>
<td>• 3-month median time between implantation and post-implantation TTE</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Possible selection bias</td>
</tr>
<tr>
<td>Klustein et al.</td>
<td>2009</td>
<td>410</td>
<td>Retrospective</td>
<td>PPM</td>
<td>Worsening of TR after PPI was not rare occurring in ~18% of the pts and observed more often in older pts, with abnormal LV relaxation and who developed pulmonary hypertension after the procedure</td>
<td>• Retrospective methodology</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>• Possible selection bias</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• TR graded visually</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Potential for intra-observer and inter-observer variability→unmeasured cofounder</td>
</tr>
<tr>
<td>Vaturi et al.</td>
<td>2010</td>
<td>23</td>
<td>Prospective</td>
<td>PPM</td>
<td>RV pacing is associated with an ↑ in TR severity</td>
<td>• Small sample</td>
</tr>
</tbody>
</table>

Fig. 8. Nuclear-powered intracardiac pacemaker.
External source of energy
(EBR Systems, Inc., Sunnyvale, California)

Diagram of the investigational device system consisting of an ultrasound generator and transmitter, a data collection instrumentation including an electrophysiology recording system, and an electrophysiology laboratory. Connections to the distal and proximal electrodes were made using leads and storage oscilloscopes.

Table 1: Electrical and Ultrasound Pacing Parameters of All Cardiac Chambers Evaluated

<table>
<thead>
<tr>
<th>Chamber</th>
<th>Electrical pacing</th>
<th>US mediated pacing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>US</td>
</tr>
<tr>
<td>VI</td>
<td>V6</td>
<td></td>
</tr>
<tr>
<td>ABP (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Leadless systems for right ventricle pacing

**St. Jude Medical Nanostim™ leadless pacemaker (LCP)**
- Available in 2012
- VVI(R)
- Screw-in helix

**Medtronic Micra™ Transcatheter Pacing System (TPS)**
- Available in 2013
- VVI(R)
- Self-expanding nitinol tines
Battery depletion, removal of the leadless pacemaker may be exist for the removal of chronic implanted systems. In the event of after implantation or if devices need to be retrieved. To date no data for recapturing the systems if repositioning becomes necessary. However, a new technology is optimizing both energy consumption and the electrode/penetration aspects of the three systems mentioned above.

Both systems offer pacing features similar to conventional VVIR cardiac pacemakers including rate response algorithms. Moreover, a different concept of leadless pacing is pursued by the ultrasound-based WiCS system (Wireless Cardiac Stimulation; EBR Systems, Sunnyvale, CA, USA). Cardiac resynchronisation therapy (CRT) is related to the lead permanently residing inside the LV. The WiCS system is intended to provide an alternative by pacing LV endocardially for CRT with a device receiving its energy from a subcutaneous ultrasound sound transmitter. Both techniques are limited by procedural issues and the long-term risk of thromboembolic events related to the lead permanently residing inside the LV. The WiCS device retrieval option remains however to be determined. How this will affect cardiac function, and how many additional systems may be implanted, remains however to be determined.

The St. Jude Medical Nanostim leadless cardiac pacemaker (reproduced with permission from St. Jude Medical Inc.) and the Micra™ transcatheter pacing system (reproduced with permission from Medtronic Inc.) are two leadless pacing systems currently available, which can be completely implanted in the right ventricle: the Nanostim device (Helix Therapeutics, Fremont, CA, USA) and the Micra™ (Medtronic Inc.) (13–15). The Micra™ leadless pacemaker is significantly smaller than conventional pacing systems, the predicted longevities are ≏10 years. This is comparable to the longevity of a standard pacemaker and is made possible by a steroid-eluting tip is incorporated to reduce inflammation. Although the primary fixation mechanism of the LCP device is a screw-in helix with a maximum penetration depth in tissue of 1.3 mm. Three nylon tines provide a secondary fixation mechanism by avoiding the anatomy of the coronary sinuses, tributaries, left ventricular endocardium/coronary sinus ostium, and more recently via puncture sites.

<table>
<thead>
<tr>
<th>Specification</th>
<th>Nanostim™ leadless cardiac pacemaker</th>
<th>Micra™ transcatheter pacing system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (cm³)</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Length (mm)</td>
<td>41.4</td>
<td>25.9</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Introducer size (French)</td>
<td>18</td>
<td>23</td>
</tr>
<tr>
<td>Primary fixation mechanism</td>
<td>Screw-in helix</td>
<td>Self-expanding nitinol tines</td>
</tr>
<tr>
<td>Secondary fixation mechanism</td>
<td>Nylon tines</td>
<td></td>
</tr>
<tr>
<td>Pacing mode</td>
<td>VVI/VVIR</td>
<td>VVI/VVIR</td>
</tr>
<tr>
<td>Rate response sensor</td>
<td>Temperature</td>
<td>Accelerometer</td>
</tr>
<tr>
<td>Energy supply Battery</td>
<td>Integrated battery</td>
<td>Integrated battery</td>
</tr>
<tr>
<td>Battery</td>
<td>Lithium carbon-monofluoride</td>
<td>Lithium silver vanadium oxide/carbon monofluoride</td>
</tr>
<tr>
<td>Battery longevity (years)</td>
<td>9.8</td>
<td>10</td>
</tr>
<tr>
<td>Rate 60 b.p.m.</td>
<td>100%/2.5 V/0.4 ms/60 b.p.m.</td>
<td>100%/1.5 V/0.24 ms/60 b.p.m.</td>
</tr>
<tr>
<td>Device retrieval option</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Telemetry</td>
<td>Conductive</td>
<td>Radio frequency</td>
</tr>
</tbody>
</table>

Implantation (LCP)

Nanostim™ (LCP) SJM clinical data: The “Leadless” trial

- Prospective multicenter non-randomized (European)
- Inclusions: >18 years, VVI(R) indication
- Exclusion: PPM dependent, mechanical TV, Pul HTN, prior implant, IVC filter
- 1° end point: SADE @ 90 days
- 2nd endpoint: implant success rate, PPM characteristics

- N=33 patients.

**Results:**
- 32 successful implants (97%).
- Complication free: 94%
- 2 SADE:
  - Tamponade $\rightarrow$ successful surgery*
  - Inadvertent LV implant $\rightarrow$ repositioned to RV in the same implant**
  - mean R-wave amplitude, pacing threshold and impedance were $8.3$ mV, $0.80$ V/0.4 ms, $773$ Ohms at implantation.

“Leadless” trial-1 year follow-up

Two patients (6%, 2 of 33) had periprocedural complications. During further follow-up no complications occurred.

On-going long term trials

1. The Leadless Observational Study
   – 1/30/14 → 3/2020
   – 5 year follow up
   – European study

2. The LEADLESS Pacemaker II IDE
   – 667 patients
   – 2/2014 → ...
   – Also looks at rate response
   – American

https://clinicaltrials.gov/
Micra™ (TPS) MDT clinical data: Micra TPS study

- **Ongoing trial***:
  - Micra Transcatheter Pacing Study + CAP
    - N=780 (140 published)
    - 12 month F/U (1.9 m published)
- **Included** 2/3 AVB, 1/3 SND
- **Results**: No SADE, mean pacing threshold was 0.51 + 0.22 V, Average R-wave was 16.1 + 5.2 mV and impedance was 650.7 + 130 ohms.
- **Battery life** = 12.6 years

Animal studies:
- Extraction was assessed in animals (18 months post implant)
- Prototype extraction tool (steerable sheaths and snares)(Cook Medical, Bloomington, IN, USA)

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Peri-procedural complications

<table>
<thead>
<tr>
<th>30 total related adverse events</th>
<th>Resulted in death, re-operation, or hospitalization?</th>
<th>Total event rate, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dysrhythmias</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient atrioventricular block</td>
<td>No</td>
<td>4 (4, 2.9)</td>
</tr>
<tr>
<td>Right bundle branch block</td>
<td>No</td>
<td>2 (2, 1.4)</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>No</td>
<td>2 (2, 1.4)</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>No</td>
<td>1 (1, 0.7)</td>
</tr>
<tr>
<td><strong>Events at device placement site</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pericardial effusion without tamponade</td>
<td>1 hospitalization prolonged &gt;48 h for both events in same patient</td>
<td>1 (1, 0.7)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pericarditis</td>
<td>No</td>
<td>2 (1, 0.7)</td>
</tr>
<tr>
<td>Non-cardiac chest pain</td>
<td>No</td>
<td>1 (1, 0.7)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>No</td>
<td>2 (2, 1.4)</td>
</tr>
<tr>
<td><strong>Events at groin puncture suite</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial pseudoaneurysm</td>
<td>1 hospitalization prolonged &gt;48 h</td>
<td>2 (2, 1.4)</td>
</tr>
<tr>
<td>Incision site haemorrhage</td>
<td>No</td>
<td>3 (3, 2.1)</td>
</tr>
<tr>
<td>Incision site haematoma</td>
<td>No</td>
<td>2 (2, 1.4)</td>
</tr>
<tr>
<td>Incision site pain</td>
<td>No</td>
<td>1 (1, 0.7)</td>
</tr>
<tr>
<td>Incisional drainage</td>
<td>No</td>
<td>1 (1, 0.7)</td>
</tr>
<tr>
<td>Vaso-vagal presyncope</td>
<td>No</td>
<td>2 (2, 1.4)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysuria following procedure</td>
<td>No</td>
<td>1 (1, 0.7)</td>
</tr>
<tr>
<td>Osteoarthritis following procedure</td>
<td></td>
<td>1 (1, 0.7)</td>
</tr>
<tr>
<td>Back pain during procedure</td>
<td>No</td>
<td>1 (1, 0.7)</td>
</tr>
</tbody>
</table>

WiCS™ clinical data: Wise-CRT study

- Non-randomized, safety/performance (1 month) + efficacy (6 months) (N=17).
- Only able to implant in 13 patients.
- Study was terminated.
- BiV pacing documented in 83% and clinical efficacy in 92%.

Issues to be considered

• Safety
  – Implantation complication
    • Venous access
    • Embolization
    • Perforation
• Retrieval/extraction of chronic devices
• Implantation of multiple devices
• Rate response characteristics (LCP)
THANK YOU
Stem Cell Based Biological Pacemakers

Rate response in LCP