Cardiac Resynchronization Therapy for Heart Block

Jonathan S. Steinberg, MD
Director, Arrhythmia Institute
Valley Health System
New York, NY and Ridgewood, NJ
### Indications for Permanent Pacing

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Sinus node disease. Pacing is indicated when symptoms can clearly be attributed to bradycardia.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>2) Sinus node disease. Pacing may be indicated when symptoms are likely to be due to bradycardia, even if the evidence is not conclusive.</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>3) Sinus node disease. Pacing is not indicated in patients with SB which is asymptomatic or due to reversible causes.</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>4) Acquired AV block. Pacing is indicated in patients with third- or second-degree type 2 AV block irrespective of symptoms.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>5) Acquired AV block. Pacing should be considered in patients with second-degree type 1 AV block which causes symptoms or is found to be located at intra- or infra-His levels at EPS.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>6) Acquired AV block. Pacing is not indicated in patients with AV block which is due to reversible causes.</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>
Once pacing indicated, does device selection and programming matter?
• The first-order pacing goal was resolution of bradycardia – atrial leads were added to establish AV synchrony.

• Pacing leads were designed for easy and reliable delivery to the RV apex, RA appendage – where the position was considered convenient and stable after years of clinical practice.
Relationship of Ventricular Pacing to New/Worsened Heart Failure Outcome in SSS PPM Patients (MOST)

Cum%Vp at 30 days and subsequent HFH events

Cum%Vp <= 40
Cum%Vp > 40

P=0.047

Sweeney et al, Circulation 2003
Risk of HF Relative to Mode/%Pacing (MOST)
Death or First Hospitalization for New/Worsened CHF in Diverse ICD Patients (DAVID)

Cumulative Probability

P ~ 0.03

VP = 3%

VP = 60%

Months of Follow-up

N at risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Initial</th>
<th>Follow-up 6</th>
<th>Follow-up 12</th>
<th>Follow-up 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDDR-70</td>
<td>250</td>
<td>159</td>
<td>76</td>
<td>21</td>
</tr>
<tr>
<td>VVI-40</td>
<td>256</td>
<td>158</td>
<td>90</td>
<td>25</td>
</tr>
</tbody>
</table>

Wilkoff et al, Cardiac Electrophysiology Review 2003
Relationship of Ventricular Pacing to New/Worsened CHF in Primary Prevention ICD Patients (MADIT II)

Steinberg et al, JCE 2005
Relationship of Ventricular Pacing to ICD Therapy for VT/VF (MADIT II)

Steinberg et al, JCE 2005
Decline in Normal Ventricular Function With RVP?

Nahlawi et al, JACC 2004
Mechanisms Underlying the Deleterious Effects of RV Apical Pacing

- Intraventricular conduction delay
- LV mechanical and electrical dyssynchrony
- LV remodeling
- Abnormal myocardial histopathology
- LV systolic dysfunction
- Overt congestive heart failure
- Myocardial perfusion defects
- Mitral regurgitation
- Left atrial dilation
- Increased atrial fibrillation
- Promotion of ventricular arrhythmias
- Activation of sympathetic nervous system
Demonstration of Pacing-Induced Dyssynchrony

Native

RV apical pacing
Summary of Potential Harm from Chronic RVP

• Observed in diverse patient device groups
• Dose effect, ie more pacing associated with more harm
• Patients with more baseline LV dysfunction most vulnerable
• Multitude of plausible mechanisms for harm, and individuals may be affected differently
• Clinical manifest harm follows preclinical measures of ventricular dysfunction, ie opportunity for preemption
Principles for Device Selection and Programming

- Almost all PPM patients who are not in permanent AF will receive a dual chamber device (RA/RV)
- ICD patients often receive single chamber device unless independent need for pacing
- If AV conduction is intact, avoid unnecessary RV pacing
  - Longer AV intervals
  - Algorithms to avoid RV pacing
  - Back-up pacing only for ICD patients
- In general, avoid programming to AAI(R) mode and/or extremely long AV intervals
But in many patients, continuous ventricular pacing is unavoidable. How can deleterious effects of RVP be mitigated?
ECG of Paced QRS Complex
**CRT Indications in Patients With Severe LVD**

**Primary Endpoint**
(All-Cause Mortality or Unplanned Hosp. for Major CVS Event)

HR 0.63 (95% CI: 0.51 to 0.77)

CRT = 159 (38.9%)
Medical = 224 (55.4%)

Mean Follow-up 29.4 months (range 18.0 - 44.7)

Cleland et al, NEJM 2005
No difference in:
- 6 min hall walk
- SF-36 QoL
- Heart failure hospitalizations
**Study Purpose and Objectives**

**Purpose:** Biventricular pacing is superior to RV apical pacing in patients with AV block and LVEF ≤50% who require ventricular pacing

**Endpoints:**

**Primary:** Composite of:

- All-cause mortality,
- HF-related urgent care, defined as
  - HF hospitalization requiring IV therapy, or
  - Any unplanned visit requiring intravenous HF therapy, and
- Increase in left ventricular end systolic volume index (LVESVI) >15%

**Key Secondary:** All-cause mortality,

All-cause mortality/HF hospitalization,

HF hospitalization
Acknowledgments

Steering Committee
Curtis AB (Principal Investigator), Adamson PB, Chung ES, St. John Sutton MG, Worley SJ

Echo Core Lab
St. John Sutton MG, Plappert T

Adverse Events Advisory Committee
Boehmer JP, Meyer TE (Chair), Smith AL, De Lurgio DB

Data Monitoring Committee
Steinberg JS (Chair), DeMarco T, Elkayam U, Louis TA (Statistician)

Investigators
Canada: Rinne C, Thibault B

Sponsor
Medtronic Inc.

Clinical Trials.gov Identifier: NCT00267098

Caution: Use of CRT devices for AV block and systolic dysfunction patients without ventricular dyssynchrony is not an approved use in the United States.

BLOCK HF
**Study Design**

- **Implant (CRT-P/D)**
- **Establish OMT (30-60 days)**
- **Randomize 1:1**
  - **Control:** RV pacing
  - **Treatment:** BiV pacing
  - **Double-Blind**
  - **Follow-up Every 3 months**

**Eligibility Criteria**

- AV block necessitating pacing
- Left ventricular ejection fraction (LVEF) < 50%
- NYHA functional class I, II or III
- Absence of a Class I indication for resynchronization therapy
- No previous pacemaker or implantable cardioverter defibrillator (ICD)
- Echocardiography performed at Randomization, 6, 12, 18 and 24 months

**Notes:**
- OMT=optimal medical therapy
- CRT-P=cardiac resynchronization therapy pacemaker
- CRT-D=CRT defibrillator
Study Flow Diagram

Enrollment
918 Assessed for eligibility

Allocation
691 Randomized 1:1

349 Allocated to Biventricular Pacing
346 Received allocated intervention
3 Did not receive allocated intervention

342 Allocated to Right Ventricular Pacing
342 Received allocated intervention

Follow-up
52 Exited/lost to follow-up
75 Deaths
13 Crossed over to Right Ventricular Pacing
3 Met primary endpoint prior to crossover

50 Exited/lost to follow-up
90 Deaths
84 Crossed over to Biventricular Pacing
50 Met primary endpoint prior to crossover

Analysis
349 Analyzed
83 Censored for primary endpoint due to missing LVESVI data

342 Analyzed
71 Censored for primary endpoint due to missing LVESVI data

227 Subjects not randomized:
95 Subjects for whom inclusion criteria not met (e.g., AV conduction testing criteria not met prior to implant)
14 Subject withdrawals prior to implant
51 Unsuccessful implants
67 Implanted subjects not randomized
## Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>CRT-P BiV (N=243)</th>
<th>CRT-P RV (N=241)</th>
<th>CRT-D BiV (N=106)</th>
<th>CRT-D RV (N=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Male</td>
<td>75%</td>
<td>70%</td>
<td>82%</td>
<td>80%</td>
</tr>
<tr>
<td>Age, years</td>
<td>74 ± 10</td>
<td>74 ± 11</td>
<td>72 ± 9</td>
<td>71 ± 10</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>43 ± 7</td>
<td>43 ± 7</td>
<td>33 ± 8</td>
<td>33 ± 8</td>
</tr>
<tr>
<td>Heart Rate, beats/min</td>
<td>69 ± 23</td>
<td>69 ± 24</td>
<td>68 ± 17</td>
<td>69 ± 17</td>
</tr>
<tr>
<td>QRS Duration, ms</td>
<td>125 ± 33</td>
<td>125 ± 31</td>
<td>123 ± 30</td>
<td>119 ± 30</td>
</tr>
<tr>
<td>NYHA I</td>
<td>14%</td>
<td>20%</td>
<td>10%</td>
<td>16%</td>
</tr>
<tr>
<td>NYHA II</td>
<td>58%</td>
<td>52%</td>
<td>63%</td>
<td>57%</td>
</tr>
<tr>
<td>NYHA III</td>
<td>27%</td>
<td>28%</td>
<td>26%</td>
<td>27%</td>
</tr>
<tr>
<td>Left Bundle Branch Block</td>
<td>35%</td>
<td>31%</td>
<td>35%</td>
<td>27%</td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td>39%</td>
<td>38%</td>
<td>63%</td>
<td>58%</td>
</tr>
<tr>
<td>1st Degree AV Block</td>
<td>17%</td>
<td>15%</td>
<td>27%</td>
<td>31%</td>
</tr>
<tr>
<td>2nd Degree AV Block</td>
<td>33%</td>
<td>29%</td>
<td>33%</td>
<td>38%</td>
</tr>
<tr>
<td>3rd Degree AV Block</td>
<td>49%</td>
<td>56%</td>
<td>40%</td>
<td>32%</td>
</tr>
<tr>
<td>ACE Inhibitor/ARB at Randomization</td>
<td>71%</td>
<td>74%</td>
<td>83%</td>
<td>88%</td>
</tr>
<tr>
<td>Beta Blocker at Randomization</td>
<td>75%</td>
<td>78%</td>
<td>92%</td>
<td>92%</td>
</tr>
<tr>
<td>Diuretics at Randomization</td>
<td>64%</td>
<td>66%</td>
<td>72%</td>
<td>70%</td>
</tr>
</tbody>
</table>
## Primary Endpoint Results: Mortality/HF Urgent Care/LVESVI

### All Randomized Subjects

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Estimated HR (95% CI)</th>
<th>Probability HR &lt; 1</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Randomized Subjects</td>
<td>0.74 (0.60, 0.90)</td>
<td>0.9978</td>
<td>0.9775</td>
</tr>
</tbody>
</table>

### CRT-P Only

<table>
<thead>
<tr>
<th></th>
<th>Estimated HR (95% CI)</th>
<th>Probability HR &lt; 1</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT-P Only</td>
<td>0.73 (0.58, 0.91)</td>
<td>0.9978</td>
<td>0.9775</td>
</tr>
</tbody>
</table>

### CRT-D Only

<table>
<thead>
<tr>
<th></th>
<th>Estimated HR (95% CI)</th>
<th>Probability HR &lt; 1</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT-D Only</td>
<td>0.75 (0.57, 1.02)</td>
<td>0.9978</td>
<td>0.9775</td>
</tr>
</tbody>
</table>

### Event-Free Rate (%)

<table>
<thead>
<tr>
<th>Number of Months</th>
<th>BiV Arm</th>
<th>RV Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>87</td>
<td>62</td>
</tr>
<tr>
<td>24</td>
<td>62</td>
<td>39</td>
</tr>
<tr>
<td>36</td>
<td>36</td>
<td>28</td>
</tr>
<tr>
<td>48</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>60</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>72</td>
<td>3</td>
<td>10</td>
</tr>
</tbody>
</table>

### Number at Risk

<table>
<thead>
<tr>
<th>Number at Risk</th>
<th>BiV: 349</th>
<th>RV: 342</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>161</td>
<td>126</td>
</tr>
<tr>
<td>12</td>
<td>87</td>
<td>59</td>
</tr>
<tr>
<td>24</td>
<td>62</td>
<td>39</td>
</tr>
<tr>
<td>36</td>
<td>36</td>
<td>28</td>
</tr>
<tr>
<td>48</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>60</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>72</td>
<td>3</td>
<td>10</td>
</tr>
</tbody>
</table>

### Graph

- **BiV Arm**
- **RV Arm**

The graph shows the event-free rate over time with a log-log scale for both BiV and RV arms, illustrating the survival analysis data.
Clinical Components of Primary Endpoint: Mortality/HF Urgent Care Visits

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Estimated HR (95% CI)</th>
<th>Probability HR &lt; 1</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Randomized Subjects</td>
<td>0.73 (0.57, 0.92)</td>
<td>0.997</td>
<td>N/A</td>
</tr>
<tr>
<td>CRT-P Only</td>
<td>0.73 (0.56, 0.94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT-D Only</td>
<td>0.73 (0.53, 1.02)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **All Randomized Subjects**: Estimated Hazard Ratio (HR) is 0.73 with a 95% Confidence Interval (CI) of (0.57, 0.92). The probability of the HR being less than 1 is 0.997, and the threshold is N/A.

- **CRT-P Only**: Estimated HR is 0.73 with a 95% CI of (0.56, 0.94).

- **CRT-D Only**: Estimated HR is 0.73 with a 95% CI of (0.53, 1.02).
Secondary Objective Results:
HF Hospitalization and Mortality

<table>
<thead>
<tr>
<th>Cohort</th>
<th>HF Hospitalization</th>
<th>Mortality</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated HR (95% CI)</td>
<td>Probability HR &lt; 1</td>
<td>Estimated HR (95% CI)</td>
</tr>
<tr>
<td>All Randomized Subjects</td>
<td>0.70 (0.52, 0.93)</td>
<td>0.9922</td>
<td>0.83 (0.61, 1.14)</td>
</tr>
</tbody>
</table>

BiV Arm

RV Arm

HF Hospitalization

Mortality

Event-Free Rate (%)
**Strengths and Limitations**

**STRENGTHS:**
- Prospective, randomized, double-blind control design
- Largest, longest follow-up trial to date
- First to show difference in outcomes in AV block and LV systolic dysfunction patients with BiV vs. RV pacing

**LIMITATIONS:**
- Long enrollment duration
- All patients received CRT systems
- Censoring due to missing LVESVI in primary objective
- Crossover imbalance between arms:
  - 24.6% crossed over from RV to BiV
  - 4.6% crossed over from BiV to RV
Conclusions

• In patients with AV block and LV systolic dysfunction (LVEF < 50%), BiV pacing compared to RV pacing leads to a significant 26% reduction in the combined endpoint of mortality, heart-failure related urgent care, and increase in LVESVI.

• Furthermore, there is a 27% relative risk reduction in the composite endpoint of heart-failure urgent care and all-cause mortality.
### Packer Clinical Composite Score at 6 Months

<table>
<thead>
<tr>
<th>Episode Type</th>
<th>Number(%) of Subjects</th>
<th>BIV Arm (N=349)</th>
<th>RV Arm (N=342)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Worsened</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>10 (2.9%)</td>
<td>16 (4.7%)</td>
<td></td>
</tr>
<tr>
<td>HF Hospitalization</td>
<td>18 (5.2%)</td>
<td>32 (9.4%)</td>
<td></td>
</tr>
<tr>
<td>Therapy Discontinuation for Worsening HF</td>
<td>0 (0%)</td>
<td>12 (3.5%)</td>
<td></td>
</tr>
<tr>
<td>Worsened NYHA</td>
<td>50 (14.3%)</td>
<td>34 (9.9%)</td>
<td></td>
</tr>
<tr>
<td>Moderately/Markedly Worse Global Assessment</td>
<td>4 (1.1%)</td>
<td>2 (0.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Unchanged</strong></td>
<td>83 (23.8%)</td>
<td>113 (33.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Improved</strong></td>
<td>184 (52.7%)</td>
<td>133 (38.9%)</td>
<td></td>
</tr>
<tr>
<td>Global Assessment &amp; NYHA</td>
<td>37 (10.6%)</td>
<td>26 (7.6%)</td>
<td></td>
</tr>
<tr>
<td>Global Assessment Only</td>
<td>126 (36.1%)</td>
<td>91 (26.6%)</td>
<td></td>
</tr>
<tr>
<td>NYHA Only</td>
<td>21 (6%)</td>
<td>16 (4.7%)</td>
<td></td>
</tr>
</tbody>
</table>
Change in NYHA Class from Baseline

BIV arm had significantly better improvement at 12 months

PP=0.591

PP=0.986

PP=0.726

PP=0.701

Worsened by 2 Classes
Worsened by 1 Class
Unchanged
Improved by 1 Class
Improved by 2 Classes

BIV  RV
6 Months N=605
12 Months N=559
18 Months N=492
24 Months N=439

Percentage of Subjects (%)
Improvement in Quality of Life from Baseline

Significant difference seen at 6 and 12 months (PP > 0.95)
For patients with AV block and systolic dysfunction, BIV pacing not only reduces the risk of mortality/morbidity, but also leads to better clinical outcomes and improved patient quality of life and HF status.
What About Patients With Preexisting RV Pacemakers? An Opportunity for Intervention at Generator Change?

- 50 patients with RV PPM and >80% RVP at time of generator replacement
- LVEF < 50% but no CHF
- Randomized to CRT-P upgrade vs simple generator change
- CRT-P patients had better exercise capacity and QoL, lower BNP and fewer hospitalization days
- But required longer procedure and fluoroscopy times

Gierula et al, Europace 2013
Based on BLOCK HF and proposed indications, panel voted:

- 6-1 that CRT-P device is safe
- 7-0 that CRT-P device is effective
- But 3-3-1 that benefits outweigh risks
- Tiebreaker by chairman brought final vote to 4-3-1
- Panel stipulated that indications should be changed to eliminate patients without AVB and that there be “verifiable confidence that ventricular pacing is needed in this patient most of the time”
- Final FDA decision is pending
Thank you!