Dyssynchrony: What Pacemakers, PVCs, and Bundle Branch Blocks Have in Common

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What is Dyssynchrony?
The Cardiac Conduction System

- Sinoatrial (SA) Node
- Atrioventricular (AV) Node
- Right Bundle Branch
- Bundle of His
- Left Bundle Branch
- Left Anterior Division
- Left Posterior Division
- Purkinje Fibres
Cardiac Resynchronization Therapy (CRT)

- Most effective for patients with a LBBB or chronic RV pacing.
Benefits of CARDIAC RE-SYNCHRONIZATION (CRT)

\[
NNT \times \text{years} = \frac{100}{(\% \text{Mortality in Control Group} - \% \text{Mortality in Treatment Group})}
\]

<table>
<thead>
<tr>
<th>CRT</th>
<th>ICD</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
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<td>11</td>
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<td>20</td>
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<td>29</td>
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<td>37</td>
</tr>
<tr>
<td>56</td>
<td></td>
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</tbody>
</table>

Years of tested treatment:
- 1 Yr
- 5 Yr
- 2.4 Yr
- 3 Yr
- 3 Yr
- 0.8 Yr
- 3.5 Yr
- 1 Yr
- 1 Yr
- 1.5 Yr
- 2 Yr
- 4 Yr

Auricchio, Abraham. Circulation. 2004
CRT Guidelines Then & Now

ACC/AHA/HRS 2008

<table>
<thead>
<tr>
<th>Class</th>
<th>Patt.</th>
<th>QRS</th>
<th>NYHA</th>
<th>EF</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td></td>
<td>&gt;120</td>
<td>III-IV</td>
<td>&lt;35</td>
</tr>
<tr>
<td>IIA</td>
<td>&gt;120</td>
<td>III-IV</td>
<td>&lt;35</td>
<td>AF</td>
</tr>
<tr>
<td>IIA</td>
<td></td>
<td>III-IV</td>
<td>&lt;35</td>
<td>Pace</td>
</tr>
<tr>
<td>IIB</td>
<td></td>
<td>I-II</td>
<td>&lt;35</td>
<td>Pace</td>
</tr>
<tr>
<td>III</td>
<td>Life expectancy &lt; 1y</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Focused update 2012 → Current

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<tr>
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<th>QRS</th>
<th>NYHA</th>
<th>EF</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>LBBB</td>
<td>&gt;150</td>
<td>II,III,IV</td>
<td>&lt;35</td>
</tr>
<tr>
<td>IIA</td>
<td>LBBB</td>
<td>120-149</td>
<td>II,III,IV</td>
<td>&lt;35</td>
</tr>
<tr>
<td>IIA</td>
<td>nLB</td>
<td>&gt;150</td>
<td>III,IV</td>
<td>&lt;35</td>
</tr>
<tr>
<td>IIA</td>
<td></td>
<td>&lt;35</td>
<td>40%P</td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>extended to AF if ~100% paced</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td>LBBB</td>
<td>&gt;150</td>
<td>I</td>
<td>&lt;30</td>
</tr>
<tr>
<td>IIB</td>
<td>nLB</td>
<td>120-149</td>
<td>III-IV</td>
<td>&lt;35</td>
</tr>
<tr>
<td>IIB</td>
<td>nLB</td>
<td>&gt;150</td>
<td>II</td>
<td>&lt;35</td>
</tr>
<tr>
<td>III</td>
<td>nLB</td>
<td>&lt;150</td>
<td>I-II</td>
<td></td>
</tr>
</tbody>
</table>

Why the big change? ECHO-CRT

JACC. 2012;60:1297
Inclusion:
- EF<35%, QRS<130ms, NYHA III-IV
- e/o dysynchrony

Randomized 800 pts 1:1, 58 yo, QRS 105ms, LVEF 27%, mostly NYHA III.

Control: CRT-D with CRT off.

Stopped early for futility. Mean 19.4 months of follow-up.

1* Death or HF: 29% vs 25%, HR 1.2 (p 0.15)

2* Death: 11.1% vs 6.4%, HR 1.8 (p 0.02); NNH ~ 20 !!!
Patient Level Meta-analysis of CRT

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Randomization</th>
<th>Sample</th>
<th>Median follow-up(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIRACLE</td>
<td>NYHA III–IV, QRS ≥ 130 ms, EF ≤ 35%</td>
<td>1:1 (CRT-P vs. VDI-30)</td>
<td>541</td>
<td>6 months</td>
</tr>
<tr>
<td>MIRACLE ICD</td>
<td>NYHA II–IV, QRS ≥ 130 ms, EF ≤ 35%, ICD indication</td>
<td>1:1 (CRT-D vs. DDI-35)</td>
<td>555</td>
<td>6 months</td>
</tr>
<tr>
<td>CARE-HF</td>
<td>NYHA III–IV, QRS ≥ 120 ms, EF ≤ 35%</td>
<td>1:1 (CRT-P vs. OMT)</td>
<td>813</td>
<td>29 months (35 months for mortality)</td>
</tr>
<tr>
<td>REVERSE</td>
<td>NYHA I–II, QRS ≥ 120 ms, EF ≤ 40%</td>
<td>2:1 (CRT ± D vs. VVI-35)</td>
<td>610</td>
<td>12 months (24 months, EU cohort)</td>
</tr>
<tr>
<td>RAFT</td>
<td>NYHA II–III, QRS ≥ 120 ms (pQRS ≥ 200 ms), EF ≤ 30%</td>
<td>1:1 (CRT-D vs. ICD)</td>
<td>1798</td>
<td>40 months</td>
</tr>
</tbody>
</table>

\(^a\) Median follow-up time varies depending on the specific endpoint.

Cleland et al. EHJ. 2013;34:3547
Why would CRT ever be harmful?

Because it is better than when it still works well enough.

Cardiovasc Res. 2004 Jul 1;63(1):77
Shifting gears ➔ Pacemakers

Pacemaker Insertion

Single chamber

Dual chamber

Biventricular

Right ventricular apical pacing

Asynchronous electrical activation

Mechanical dysynchrony
Redistribution of work; Decreased energetics
Altered coronary arterial flow
Decreased contractility and cardiac output

Myocellular remodeling

Long term left ventricular dysfunction

Kaufman et al. Cardiol Young. 2008
RV PACING CARDIOMYOPATHY IS MOSTLY REVERSIBLE WITH UPGRADE TO CRT

CENTRAL ILLUSTRATION: Improvement in LVEF After CRT Upgrade

A) PICM, LVEF<50

B) PICM, LVEF<35

C) Development of severe PICM with LVEF < 35% → Upgrade to CRT pacer → LVEF ≥ 35% → Consider CRT defibrillator

72% "SUPER-RESPONSE" TO CRT IN THIS POPULATION

1 year response period

Can RV Pacing Cardiomyopathy be Avoided?

S/p permanent His Bundle PPM

Univ. of Minn Geisinger Health
Why pace the His?

- We know for certain that chronic RV pacing is harmful: carries a risk of decline in LVEF & symptomatic HF.

- BIV pacing (compared to RV) mitigates harm in patients with a high ventricular pacing burden and even mildly depressed LVSF (50%) as seen in BLOCK-HF.

- Even BIV pacing is harmful for patients with a narrow QRS: increase in HF endpoints and mortality in ECHO-CRT.

Narrow Native QRS $\gg$ BIV Pacing $\gg$ RV pacing

- HBP at least as good as BIV; ? Better than BIV
  - Good BIV bailout; reports of LBBB reversal
  - Thresholds are an issue
  - Technical challenges should improve
Why pace the His Bundle?

**Figure 2: Potential of His Bundle Pacing**

<table>
<thead>
<tr>
<th>A</th>
<th>Initial cardiac activation (Narrow or broad QRS)</th>
<th>B</th>
<th>Current pacing solutions (Never narrow QRS)</th>
<th>C</th>
<th>His bundle pacing solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narrow QRS</td>
<td><img src="image" alt="Narrow QRS" /></td>
<td>Activation prolonged</td>
<td><img src="image" alt="Activation prolonged" /></td>
<td>Ventricular activation preserved</td>
<td></td>
</tr>
<tr>
<td>LBBB</td>
<td><img src="image" alt="LBBB" /></td>
<td>Activation moderately improved</td>
<td><img src="image" alt="Activation improved" /></td>
<td>Ventricular activation restored</td>
<td></td>
</tr>
</tbody>
</table>

Ali et al. AER. 2018
Outcome Data on His Bundle Pacing (HBP)?

- Not an RCT (2 hospitals)
  - 304 HBP / 332 attempted
  - Compared all to RVP
- Composite endpoint driven by HF hospitalization
- Favorable trend in mortality (p 0.06).

Technical Challenges & Limitations

- Elevated Thresholds (mixed data), problem especially in younger patients
- ~10% Failure rate at experienced centers
- Equipment is getting better
What does any of this have to do with PVCs?

- Alterations in intracellular calcium and membrane ionic currents
- Hemodynamic impairment
- Alterations in heart rate dynamics
- Myocardial and peripheral vascular autonomic dysregulation
- Tachycardia-induced cardiomyopathy
- Ventricular dyssynchrony
- Increased oxygen consumption

Cha et al. Circ EP. 2012
Risk Correlates with Burden & Width

Cha et al. Circ EP. 2012
Carballeira et al. Heart Rhythm. 2014
PVC Ablation & Improvement in LVSF

Figure 3  Left: Change of ejection fraction (EF) in patients with successful ablation. Right: Change of EF in patients with unsuccessful ablation.

Figure 4  Left: Change in premature ventricular complex (PVC) burden in patients with change of ejection fraction (EF) < 10%. Right: Change in PVC burden in patients with change of EF ≥ 10%.
Dramatic Improvement in New-onset NICM with High Burden

- 3 months of palpitations
- 1 month of dyspnea
- LVEF 25% \(\rightarrow\) 50% post ablation
3 Take Home Messages

• CRT is an extremely effective therapy for the right patients
  • BUT, there is a harm signal associated with CRT in patients with a borderline QRS, not just lack of benefit, but actual harm (NNH~20).

• His Bundle Pacing is probably going to be a big thing going forward as technical challenges are overcome.

• Patients with a cardiomyopathy (especially NICM) and a high PVC burden should have PVCs suppressed either pharmacologically or with ablation when appropriate.