Cardiac Resynchronization Therapy Guidelines and Missing Groups

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Disclosures

• Director: Avicenna Medical Systems
• Consultant: Boston Scientific, Medtronic
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• Yes, I am from the University of Michigan
Objectives

• Review the basis for the current Guidelines for CRT-D and CRT-P

• Identify potential new populations for CRT therapy.

Cardiac Resynchronization Therapy (CRT)

Proposed mechanism for CRT

![Diagram showing proposed mechanism for CRT]

Effects of Dyssynchrony and CRT

<table>
<thead>
<tr>
<th></th>
<th>Dyssynchrony</th>
<th>Ressynchrony</th>
</tr>
</thead>
<tbody>
<tr>
<td>Action Potential Duration: Lat LV</td>
<td>Increased</td>
<td>Partially Normalized</td>
</tr>
<tr>
<td>Regional hypertrophy</td>
<td>Increased</td>
<td>Normalized</td>
</tr>
<tr>
<td>Heterogeneous Glucose Uptake</td>
<td>Present</td>
<td>Normalized</td>
</tr>
<tr>
<td>B-adrenergic signaling</td>
<td>Depressed</td>
<td>Improved</td>
</tr>
<tr>
<td>Ca sensitivity</td>
<td>Reduced</td>
<td>Improved</td>
</tr>
<tr>
<td>Fetal gene program</td>
<td>Activated</td>
<td>Deactivated</td>
</tr>
<tr>
<td>Stress Kinases</td>
<td>Upregulated</td>
<td>Normalized</td>
</tr>
<tr>
<td>Connexin 43</td>
<td>Downregulated</td>
<td>Normalized</td>
</tr>
<tr>
<td>Ca handling proteins expression</td>
<td>Heterogenous</td>
<td>Normalized</td>
</tr>
</tbody>
</table>

Adapted from stahlberg, et al. Scandinavian Cardiovascular Journal, 50:5-6, 282-292
### ACC Guidelines: 2008 vs 2012 (Class I, IIA)

<table>
<thead>
<tr>
<th>Class (Evidence)</th>
<th>2008</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>LVEF &lt;35%, a QRS &gt;120 CRT, NSR, NYHA III, ambulatory IV, (A)</td>
<td>LBBB QRS&gt;150 ms, NYHA II, III, IV (A for III, IV, B for II)</td>
</tr>
<tr>
<td>IIA</td>
<td>1. LVEF &lt;35%, QRS &gt;120 ms, AF NYHA III or ambulatory Class IV (B) 2. LVEF &lt;35% NYHA Class III or ambulatory Class IV Frequent Pacing, (C)</td>
<td>1. LVEF &lt;35%, NSR, LBBB QRS 120-149 ms, NYHA class II, III, or ambulatory IV (B) 2. LVEF &lt;35%, NSR, non-LBBB pattern QRS &gt;150 ms, NYHA class III/ambulatory class IV (A) 3. LVEF &lt;35% ventricular pacing near 100% (B) 4. LVEF &lt; 35% and Anticipated pacing &gt; 40% (C)</td>
</tr>
</tbody>
</table>

### ACC Guidelines 2008 vs 2012 (Class IIb, III)

<table>
<thead>
<tr>
<th>Class</th>
<th>2008</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>1. LVEF &lt;35% NYHA I or II Anticipated frequent RV pacing, (C)</td>
<td>1. LVEF &lt;30%, Isch CM, NSR, LBBB QRS&gt;150 ms NYHA class I (C) 2. LVEF &lt;35%, NSR non-LBBB QRS 120 - 149 ms, NYHA III, IV (B) 3. LVEF &lt;35%, NSR non-LBBB QRS &gt;150 ms, NYHA class II (B)</td>
</tr>
<tr>
<td>III</td>
<td>1. asymptomatic patients with reduced LVEF, no pacing (B) 2. Poor non cardiac functional status or life expectancy</td>
<td>1. non-LBBB pattern QRS&lt; 150 ms NYHA I, II (B) 2. Comorbidities and/or frailty limit survival &lt;1 year (C)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>European guidelines</th>
<th>U.S. guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary prevention ICD in NYHA class II, III, and IV patients with EF ≤ 35%</td>
<td>No Recommendation in NYHA I patients</td>
<td>Class IIa recommendation, Level of Evidence B</td>
</tr>
<tr>
<td>CRT in NYHA class III/IV patients with LBBB, QRS duration 120-150 ms, and EF ≤ 35%</td>
<td>Class I recommendation, Level of Evidence B</td>
<td>Class IIa recommendation, Level of Evidence B</td>
</tr>
<tr>
<td>CRT in NYHA class II patients with LBBB, QRS &gt; 130 ms, and EF ≥ 35%</td>
<td>Class I recommendation, Level of Evidence A</td>
<td>Class IIa recommendation, Level of Evidence B</td>
</tr>
<tr>
<td>CRT-D in NYHA class II patients with LBBB, QRS &gt; 150 ms, and EF &lt; 35%</td>
<td>Class I recommendation, Level of Evidence A</td>
<td>Class IIb recommendation, Level of Evidence B</td>
</tr>
<tr>
<td>CRT in NYHA class II non-LBBB patients, QRS 120-149 ms, and EF ≤ 35%</td>
<td>No implantation of CRT</td>
<td>Class IIb recommendation, Level of Evidence B</td>
</tr>
<tr>
<td>CRT in NYHA class I patients with EF ≤ 35%</td>
<td>No mention</td>
<td>Those with LBBB and a QRS &gt; 150 ms are indicated for CRT as Class IIb Recommendation, Level of Evidence C</td>
</tr>
</tbody>
</table>

Kutyifa V, et al. HRJ, 2017

What is the basis for these guidelines?

CRT for NYHA III, IV

- 2002 MIRACLE trial (Abraham, et al. NEJM)
  - Compared CRT (QRS>130) vs conventional therapy.
  - Significant improvement in 6 min walk, NYHA class

- 2003: MIRACLE ICD (Young, et al, JAMA)
  - Compared ICD vs CRT
  - Significant improvements Quality of Life scores and NYHA class

  - Compared CRT-P vs CRT-D vs non device
  - Similar findings in 6MW, NYHA
  - Significant improvement in primary endpoint (all cause mortality + heart failure hospitalizations)
  - No difference (CRT-P vs CRT-D)

- 2005: CARE- HF (Cleland, et al. NEJM)
  - CRT-P vs medical therapy (EF<0.35, QRS > 120)
  - 37% HR reduction in combined mortality-hospitalization endpoint
  - HR 0.64 for death in the CRT-P group
CRT and NYHA I, II Heart Failure

- 2008: REVERSE (Linde, at al., JACC)
  - NYHA I, II, QRS>120 n=610
  - Composite Primary endpoint: improved, worsened, no change
  - NS improvement of primary endpoint
  - Significant improvement in LV volume parameters
  - 53% RR reduction in first time HF hospitalization

  - NYHA I, II, QRS>130
  - Combined endpoint of all cause mortality, HF event
  - HR 0.66 in the treatment group
  - Benefits primarily seen in HF event reductions

CRT for chronically paced patient

- 2010: RAFT (Tang AS, et al, NEJM)
  - Included RV paced patients all cause mortality hospitalizations
  - HR 0.75 in the CRT group
  - Subset Analysis: no advantage with CRT in the pacemaker subset

- COMBAT, HOBIPACE
  - Smaller study populations
  - Improvement in QOL, LV dimensions, 6 min walk

- 2015:Block HF (Curtis A, et al, NEJM)
  - Primary end point was all cause mortality, HF event or change in ESV
  - Significant difference in CRT group (53% v 64%)
Appropriate Use (2013)

Nonischemic Cardiomyopathy, Sinus Rhythm, and LVEF ≤35%

QRS ≤120
- LBBB
- Non-LBBB
  - NYHA Class I/II
  - NYHA Class III-amb. IV

QRS 120-149
- LBBB
- Non-LBBB
  - NYHA Class I/II
  - NYHA Class III-amb. IV

QRS ≥150
- LBBB
- Non-LBBB
  - NYHA Class I/II
  - NYHA Class III-amb. IV

Heart Rhythm, Vol 10, No 4, April 2013

Appropriate Use: RV Pacing (2013)

Intrinsic Narrow QRS

LVEF ≤35%
- RV pacing anticipated ≤40%
- NYHA Class I/II
- M

LVEF >35%
- RV pacing anticipated >40%
- NYHA Class III-amb. IV
- A

Heart Rhythm, Vol 10, No 4, April 2013
Are there untapped groups that could benefit from CRT?

### CRT: Hypertrophic Cardiomyopathy (HOCM)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>3 months</th>
<th>1 year</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA class</td>
<td>3.2 ± 0.6</td>
<td>1.9 ± 0.3*</td>
<td>1.4 ± 0.5†</td>
<td>&lt;.05*</td>
</tr>
<tr>
<td>Six-minute walk test (m)</td>
<td>349 ± 116</td>
<td>464 ± 144*</td>
<td>517 ± 106†</td>
<td>&lt;.05*</td>
</tr>
<tr>
<td>AVD LV-RV timing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 had CRT (2 simultaneous, 4 LV early)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 LV only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 RV only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVD: 65±11 msec</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echo guided pacing optimization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>356 ± 110</td>
<td>315 ± 70*</td>
<td>284 ± 42†</td>
<td>&lt;.05*</td>
</tr>
<tr>
<td>Resting LVOT gradient (mmHg)</td>
<td>74 ± 23</td>
<td>40 ± 16*</td>
<td>28 ± 17†</td>
<td>&lt;.05*</td>
</tr>
<tr>
<td>Interventricular septum (mm)</td>
<td>20.5 ± 5.2</td>
<td>18.4 ± 4.1*</td>
<td>17.3 ± 4.6†</td>
<td>&lt;.05*</td>
</tr>
<tr>
<td>Posterior wall (mm)</td>
<td>15 ± 2.9</td>
<td>14.2 ± 1.1*</td>
<td>12.7 ± 1.3†</td>
<td>&lt;.05†</td>
</tr>
<tr>
<td>LV end-diastolic diameter (mm)</td>
<td>45.1 ± 5.9</td>
<td>45 ± 6.3*</td>
<td>44.2 ± 7.9†</td>
<td>&lt;.05†</td>
</tr>
<tr>
<td>Mitral regurgitation (grade)</td>
<td>2.2 ± 0.8</td>
<td>1.7 ± 0.7*</td>
<td>0.9 ± 0.4†</td>
<td>&lt;.05†</td>
</tr>
</tbody>
</table>

CRT and HOCM

• 13 patients with HOCM and normal EF

• Echo-guided optimization
  • AVD
  • LV-RV timing to reduce LVOT gradient
    • RV -30msec  8%
    • LV-RV simult 23%
    • LV -30msec 54%
    • LV -60msec 8%
    • LV only 8%


<table>
<thead>
<tr>
<th>CRT and HOCM</th>
<th>Responser (n=8)</th>
<th>Non-responders (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
</tr>
<tr>
<td>Rest LVOT gradient (mmHg)</td>
<td>96 (40/111)</td>
<td>15 (0/30)*</td>
</tr>
<tr>
<td>Provoked LVOT gradient (mmHg)</td>
<td>111 (71/149)</td>
<td>33 (0/56)*</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>60 (56/72)</td>
<td>60 (52/71)</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>45 (39/54)</td>
<td>40 (34/60)</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>12 (10/18)</td>
<td>13 (11/16)</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>71 (67/74)</td>
<td>69 (65/75)</td>
</tr>
<tr>
<td>LV radial strain (%)</td>
<td>31.4 (22.9/48.1)</td>
<td>32.1 (25.4/40.2)</td>
</tr>
<tr>
<td>LV longitudinal strain (%)</td>
<td>-17.1 (-20.0/-14.7)</td>
<td>-15.6 (-17.1/-14.7)</td>
</tr>
<tr>
<td>Septal thickness (mm)</td>
<td>24 (19/28)</td>
<td>21 (18/26)</td>
</tr>
<tr>
<td>LV posterior wall thickness (mm)</td>
<td>12 (10/13)</td>
<td>11 (10/11)*</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>358 (215/364)</td>
<td>268 (203/378)</td>
</tr>
</tbody>
</table>

CRT with preserved EF and chronic pacing

- 173 patients randomized to RV vs CRT
- Baseline EF 0.61
- Baseline LVEF 28.6ml
- 12 month follow up
- 9 patients had LVEF <45%
  - 8 were in the RV group
  - 1 were in the CRT group


HFpEF: the impact of QRS duration

- TOPCAT subset analysis (Jacobs, et al. JACC Heart Failure, 2016)
  - N= 3400 patients LVEF≥45
  - Primary Endpoints: mortality, aborted SCD, HF hospitalizations
  - Hazard Ratio QRS>120
  - RBBB: 2.1
  - LBBB:1.6
  - IVCD:1.8
  - VP:2.2
- MIRACLE-EF: NYHA II, III, QRS>130, EF 0.36-0.5
  - stopped due to low enrollment

Persistent LBBB after TAVI

Urena, et al J Am Coll Cardiol 2012;60:1743–52

RBBB masking LBBB

Conclusions

• CRT improves heart failure events, and survival
• CRT has evolved to be used in milder forms of HF and patients that chronically paced
• Future research opportunities
  • TAVI
  • HOCM
  • Subsets of patients with HFpEF
  • Subsets of patients with RBBB and low EF
Thank You

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