Cardiac Resynchronization Therapy

Expanding Indications & Optimizing Technique

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Disclosures

CONSULTING FEES / HONORARIA
– GE Healthcare,
– HeartForce Medical,
– Medtronic,
– St. Jude Medical.

RESEARCH / RESEARCH GRANTS
– GE Healthcare,
– Cambridge Heart Inc,
– HeartForce Medical,
– Medtronic,
– St. Jude Medical.
Northeast on I-90
~ 800 miles
(1,280 km)
**DINAMIT**

- N = 674
- EF ≤ 0.35 (6-40 d post-MI)
- Impaired HR variability

**IRIS**

- N = 898
- EF ≤ 0.40 (5-31 d post-MI)
- Elevated HR +/- NSVT


Combined Parameter Assessment

322 post-MI patients
serial assessment
(2-4 & 10-14 weeks)

Later testing more accurate
6-fold higher risk with
abnormal HRT + TWA

Sensitivity: 55%
Positive PV: 27%
Negative PV: 96%

Cardiac Death or Cardiac Arrest

Exner et al. JACC 2007;50:2275-84.
Risk Estimation Following Infarction: Noninvasive Evaluation: ICD efficacy

- EF 0.36 to 0.49
  - 2-14 mo. post-MI
  - ≥ 3 mo. post-revasc.
  - Not on dialysis
  - Not in permanent AF

Follow-up yearly for a mean of 5 years

Usual Care Alone

Usual Care + ICD

Holter

Abnormal TWA + HRT

Registry

REFINE ICD
Unique Features

Later timing post-MI
Unstudied, but important population
  – LVEF > 0.35
  – Markers of propensity toward a cardiac arrest
Shock reduction ICD programming
CRT - Expanding Indications & Optimizing Technique
Overview

Principles underlying CRT effectiveness
Recent CRT studies
Identifying those most likely to benefit from CRT
Issues that remain unaddressed
Pre-operative & intra-operative strategies to enhance the likelihood of response to CRT
ACC / AHA / HRS Guidelines: CRT

Class I / Level A

• EF ≤ 0.35, QRS > 120 ms, NSR & NYHA III (ambulatory IV) despite optimal medical therapy.

Class IIa / Level B

• As above with atrial fibrillation rather than NSR.

Class IIa / Level C

• Not NSR, but dependence on ventricular pacing.

Class IIb / Level C

• NYHA I or II with pacing indication & anticipated frequent ventricular pacing
Resynchronization: Mechanisms

Intraventricular Synchrony
- improved dP/dt, EF, CO & PP
- ↓ LVESV

Atrioventricular Synchrony
- ↓ MR
- ↓ LVEDV

Interventricular Synchrony
- ↑ LV diastolic filling
- ↑ RV Stroke Volume

Reverse Remodeling
- improved dP/dt, EF, CO & PP
Myocardial Contraction & Relaxation

Complex 3D phenomenon

Diffusion tensor MRI-estimates of fibre inclination angle *(canine).*

Longitudinal  Circumferential

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Hypothesis

CRT + ICD versus ICD alone will reduce the risk of death from any cause or hospitalization for heart failure in patients with mild to moderate heart failure symptoms, and a wide QRS
RAFT - Design

ICD or CRT + ICD
  – Stratified by center, atrial rhythm (permanent AF/flutter vs. sinus/atrial pacing), single vs. dual

Blinding
  – EP team aware of treatment allocation
  – HF team NOT aware of allocation
  – Patients NOT aware of allocation
RAFT - Eligibility

NYHA II or III (Class III until February 2006)

QRSd ≥ 120 ms or paced QRSd ≥ 200 ms

LVEF ≤ 0.30

1° or 2° prevention ICD indication

Optimal medical therapy for HF

Sinus rhythm or chronic AF / flutter

– Controlled ventricular rate
RAFT - Death or Hospitalization

HR (95% CI) 0.75 (0.64, 0.87)
P=0.0002

ICD-CRT
(5-yr HF-free survival rate 0.576)

ICD
(5-yr HF-free survival rate 0.487)

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Tang et al. NEJM 2010; 363:2385-95
RAFT - Death

Event-free Survival

Years of Follow-up

HR (95% CI) 0.75 (0.62, 0.91)
P=0.003

ICD-CRT
(5-yr survival rate 0.714)

ICD
(5-yr survival rate 0.654)

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Tang et al. NEJM 2010; 363:2385-95
### CRT in NYHA Class I / II: Mortality

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>CRT Group, n</th>
<th>Control Group, n</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Predominantly NYHA class I/II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIRACLE-ICD II, 2004 (36)</td>
<td>2</td>
<td>85</td>
<td>2</td>
</tr>
<tr>
<td>REVERSE, 2008 (11)</td>
<td>9</td>
<td>419</td>
<td>3</td>
</tr>
<tr>
<td>MADIT-CRT, 2009 (12)</td>
<td>74</td>
<td>1089</td>
<td>53</td>
</tr>
<tr>
<td>RAFT, 2010 (13)</td>
<td>186</td>
<td>894</td>
<td>236</td>
</tr>
<tr>
<td>Greater-EARTH, 2010 (27)</td>
<td>2</td>
<td>61</td>
<td>2</td>
</tr>
<tr>
<td>van Geldorp et al, 2010 (26)</td>
<td>0</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2567</td>
<td></td>
<td>2005</td>
</tr>
<tr>
<td>Total events</td>
<td>273</td>
<td></td>
<td>296</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; chi-square = 1.46; P = 0.83; I² = 0%
Test for overall effect: Z = 2.43; P = 0.01

Total (95% CI)

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>CRT Group, n</th>
<th>Control Group, n</th>
<th>Risk Ratio (95% CI)</th>
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<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predominantly NYHA class I/II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5080</td>
<td></td>
<td>4002</td>
</tr>
<tr>
<td>Total events</td>
<td>565</td>
<td></td>
<td>577</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; chi-square = 13.40; P = 0.94; I² = 0%
Test for overall effect: Z = 4.00; P < 0.001
Test for subgroup differences: Not applicable

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Impact of QRS Duration

Hazard Ratio (95% CI)

Intrinsic QRS duration

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Tang et al. AHA 2010
# MADIT-CRT Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Events/No. of Patients</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>294/1367</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>78/453</td>
<td></td>
</tr>
<tr>
<td><strong>NYHA class</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic I</td>
<td>53/265</td>
<td></td>
</tr>
<tr>
<td>Ischemic II</td>
<td>186/734</td>
<td></td>
</tr>
<tr>
<td>Nonischemic II</td>
<td>133/821</td>
<td></td>
</tr>
<tr>
<td><strong>QRS duration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;150 msec</td>
<td>147/645</td>
<td></td>
</tr>
<tr>
<td>≥150 msec</td>
<td>225/1175</td>
<td></td>
</tr>
<tr>
<td><strong>LVEF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤25%</td>
<td>101/646</td>
<td></td>
</tr>
<tr>
<td>&gt;25%</td>
<td>271/1174</td>
<td></td>
</tr>
<tr>
<td><strong>All patients</strong></td>
<td>372/1820</td>
<td></td>
</tr>
</tbody>
</table>

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Moss et al. NEJM 2009; 361: 1329-3
Updated Guidelines (Europe)

CRT for patients

• in NSR,

• LVEF ≤ 0.35,

• NYHA class II limitation, &

• QRSd ≥ 150 ms.
## RAFT - Complications (initial 30 d)

<table>
<thead>
<tr>
<th></th>
<th>ICD</th>
<th>ICD-CRT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemo/pneumothorax</td>
<td>8 (0.89)</td>
<td>11 (1.24)</td>
<td>0.47</td>
</tr>
<tr>
<td>Pocket hematoma</td>
<td>11 (1.22)</td>
<td>14 (1.58)</td>
<td>0.53</td>
</tr>
<tr>
<td>Pocket infection</td>
<td>16 (1.78)</td>
<td>21 (2.36)</td>
<td>0.39</td>
</tr>
<tr>
<td>Tamponade</td>
<td>2 (0.22)</td>
<td>1 (0.23)</td>
<td>1</td>
</tr>
<tr>
<td>Lead dislodgement</td>
<td>20 (2.22)</td>
<td>61 (6.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary sinus dissection</td>
<td>0 (0.0)</td>
<td>11 (1.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Device pocket revision</td>
<td>1 (0.11)</td>
<td>4 (0.45)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

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Tang et al. NEJM 2010; 363:2385-95
Rarely is it a “simple CRT upgrade”
### CRT in Patients with AF: Mortality

**Higher annual mortality** (10.8% AF vs. 7.1% NSR)

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>AF</th>
<th>SR</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leclercq (2000)</td>
<td>1.83 (0.59, 5.73)</td>
<td>5/15</td>
<td>4/22</td>
<td>6.0</td>
</tr>
<tr>
<td>Linde (2002)</td>
<td>1.14 (0.54, 2.40)</td>
<td>12/64</td>
<td>11/67</td>
<td>10.3</td>
</tr>
<tr>
<td>Molhoek (2004)</td>
<td>2.33 (0.67, 8.18)</td>
<td>7/30</td>
<td>3/30</td>
<td>5.2</td>
</tr>
<tr>
<td>Deltour (2007)</td>
<td>0.72 (0.31, 1.67)</td>
<td>7/96</td>
<td>17/167</td>
<td>9.0</td>
</tr>
<tr>
<td>Ferreira (2008)</td>
<td>7.36 (1.68, 32.25)</td>
<td>10/53</td>
<td>2/78</td>
<td>4.0</td>
</tr>
<tr>
<td>Gasparini (2008)</td>
<td>0.98 (0.72, 1.35)</td>
<td>39/243</td>
<td>170/1042</td>
<td>18.2</td>
</tr>
<tr>
<td>Khadjooi (2008)</td>
<td>1.24 (0.85, 1.81)</td>
<td>28/86</td>
<td>55/209</td>
<td>16.9</td>
</tr>
<tr>
<td>Tolosana (2008)</td>
<td>2.16 (1.23, 3.81)</td>
<td>19/126</td>
<td>24/344</td>
<td>13.2</td>
</tr>
<tr>
<td>Wilton (2009)*</td>
<td>2.09 (1.45, 3.00)</td>
<td>16/20</td>
<td>28/73</td>
<td>17.2</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>1.50 (1.08, 2.09)</td>
<td>143/733</td>
<td>314/2032</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Heterogeneity p = 0.008, I²=61.5%

**NOTE:** Weights are from random effects analysis.
RAFT - Chronic AF Patients

229 (13%) in the permanent AF strata; randomized to ICD (n = 115) or ICD + CRT (n = 114)

Freedom from death or HF hospitalization

\[ p = 0.82 \]

Healey et al., AHA 2011
CRT in Patients with RBBB: Mortality

<table>
<thead>
<tr>
<th>QRS category</th>
<th>Hazard ratio (n)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBBB</td>
<td>0.45 (1281)</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>RBBB</td>
<td>0.96 (228)</td>
<td>NS</td>
</tr>
<tr>
<td>IVCD/other</td>
<td>1.42 (309)</td>
<td>NS</td>
</tr>
</tbody>
</table>

“Physicians and patients should be aware of ... reduced benefit form CRT in patients with RBBB, and this should be factored into decision making.”
Non-response: Underlying Causes

- Subopt. AV timing
- Arrhythmia
- Anemia
- Subopt. LV lead position
- < 90% BiV Pacing
- Subopt. Medical Therapy

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# Venous Anatomy: LV Lead Choice

<table>
<thead>
<tr>
<th>Angulation &amp; Tortuosity</th>
<th>Large</th>
<th>Medium</th>
<th>Small</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Little</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Great</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Vein Size

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Reasons for Loss of LV Pacing

LV lead related complications; 67 of 1,307 pts (5.1%)

- PNS (1.6%)
- LV Lead Dislodgement (2.7%)

Exner et al., HRS 2011
Survival from LV Lead Related Complication

At 18 months, 94.7% (93.2%, 95.9%)

Pacing thresholds (at 0.5 ms pulse width)

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacing</td>
<td>1.39 ± 1.18</td>
<td>1.39 ± 0.99</td>
</tr>
<tr>
<td>Months Post-implant</td>
<td>0 3 6 9 12 15 18</td>
<td></td>
</tr>
</tbody>
</table>
Loss of CRT by LV Lead Tip Location

<table>
<thead>
<tr>
<th>Location</th>
<th>12 mon</th>
<th>18 mon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apical</td>
<td>97.7%</td>
<td>97.7%</td>
</tr>
<tr>
<td>Mid</td>
<td>95.5%</td>
<td>95.1%</td>
</tr>
<tr>
<td>Basal</td>
<td>92.7%</td>
<td>91.8%</td>
</tr>
</tbody>
</table>

Log-rank p = 0.039

Exner et al., HRS 2011
Position Matters: LV Lead Position

N = 250 consecutive patients; 20 (8%) anterior

Clinical Response

<table>
<thead>
<tr>
<th>Percent</th>
<th>Survival for 6 months and reduced NYHA over 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td></td>
</tr>
<tr>
<td>76</td>
<td></td>
</tr>
<tr>
<td>71</td>
<td></td>
</tr>
</tbody>
</table>

All-cause Mortality

<table>
<thead>
<tr>
<th>Follow-up (days)</th>
<th>Risk of death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anterior</td>
</tr>
<tr>
<td></td>
<td>Lateral</td>
</tr>
<tr>
<td></td>
<td>Posterior</td>
</tr>
</tbody>
</table>

# Long Axis LV Lead Position

<table>
<thead>
<tr>
<th>Physician</th>
<th>Base</th>
<th>Mid</th>
<th>Apex</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base</td>
<td>60</td>
<td>66</td>
<td>21</td>
<td>147 (34%)</td>
</tr>
<tr>
<td>Mid</td>
<td>43</td>
<td>150</td>
<td>84</td>
<td>277 (64%)</td>
</tr>
<tr>
<td>Apex</td>
<td>0</td>
<td>3</td>
<td>5</td>
<td>8 (1.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>103 (24%)</td>
<td>219 (51%)</td>
<td>109 (25%)</td>
<td>432 (100%)</td>
</tr>
</tbody>
</table>

**Kappa** = 0.15 (95% CI 0.08 to 0.22)

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Wilton et al. Can J Cardiol (abstract) 2011
MADIT-CRT - LV Short Axis Lead Position

N = 799 patients; extent of CRT benefit similar for anterior, lateral, or posterior position ($P = 0.7$).
Apical vs. non-apical position associated with an independently higher risk of death (HR 2.9; 95% CI 1.4-6.0; \( p = 0.004 \)).
Site of LV Pacing - Importance of Etiology

Ischemic Etiology
35% of patients have focal scar in the usual LV pacing site

Focal Scar

Circulation 2006 113:969-76

Non-ischemic Etiology
≥ 70% of peak response occurs over ~ 40% of LV free wall

Optimal Pacing Region

Circulation 2007 115:953-61

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Impact of Scar

Log-rank p=0.0013
HR: 2.30 (1.36, 4.34), p=0.0014

Speckle Tracking

N = 244
Observational
Radial strain analysis
Lead position: Chest X-ray
Mean follow-up 32 mo.
Ischemic 58%
NYHA III 90%

Ypenburg, et al. JACC 2008;52:1402–9
Proximity of LV Lead to the Latest Segment

N = 244

Observational Radial strain analysis

Lead position: Chest X-ray

Mean follow-up 32 mo.

Ischemic 58%

Ypenburg, et al. JACC 2008;52:1402–9
INCREMENTAL - Proximity to Target Site

**LV Lead Location**

- **Reached**
  - End Systolic Volume
  - Ejection fraction
  
- **Adjacent**
  - 
  - P < 0.0001

- **Remote**

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INCREMENTAL - Long-term Outcome

Mortality

Follow-up (days)

p < 0.0001

remote

adjacent

reached

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CMR Plus Clinical Assessment

Dyssynchrony, Scar & Creatinine (DSC) Index.

- DSC index <3 (3/83 [4%])
- DSC index 3 to 5 (9/30 [30%])
  HR: 11.1 (3.00 to 41.1), p=0.0003
- DSC index ≥5 (25/35 [71%])
  HR: 30.5 (9.15 to 101.8), p<0.0001

Log rank p <0.0001

Survival from cardiovascular death

Time (days)
**INTRINSIC**

- Peak atrial systole
- Diastolic MR
- PP

**PACED**

- Synchronized LV & atrial systole
- PP

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COMPANION: Changes in BP

Systolic Blood Pressure

Diastolic Blood Pressure

P-value
CRT vs. OPT
CRT-D vs. OPT

P-value
CRT vs. OPT
CRT-D vs. OPT

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NEJM 2002; 346: 1845-53
Delayed LV Sensing (Q-LV)

Retrospective analysis in SMART-AV (n = 426)

Summary - CRT

CRT is complicated, as are our patients
Reduces mortality in less symptomatic patients
Identifying patients who do not benefit is challenging (QRSd? AF? RBBB? Other?)
Pre-operative & intra-operative strategies exist to increase the likelihood of benefit
Questions / Comments?