This is What I do to Improve CRT Response for CRT Non-Responders

Michael R Gold, MD, PhD
Medical University of South Carolina
Charleston, SC

Disclosures: Steering Committees (unpaid) and Clinical Trials, Medtronic, Boston Scientific, St Jude
Nonresponders

• Most clinical studies report CRT non-responder rates of about 30%
• This percentage remained stable over two decades of trials involving both severe and mild heart failure
• However, the non-response rate is very dependent on endpoint measured and time
Nonresponder Rates
Nonresponders

Non-responders exist & magnitude of response is variable

What defines a responder vs. "non-responder"?

Status

CRT Implantation

Time

Super-Responder

Responder

"Non progressor"

Negative responders

Non-responder

Steffel & Ruschitzka, Circulation 2015
Determinants of Response:

1. THE APPROPRIATE’ PATIENT
2. VENTRICULAR LEAD PLACEMENT
3. OPTIMAL PROGRAMMING & FOLLOW UP
First Principles: Prevent non-responders by patient selection.

- Clinical predictors of response rate
  - Women
  - Non-ischemic Cardiomyopathy
  - QRS duration
  - LBBB

- Clinical predictor of poor response
  - Inotropic dependent
  - Scar
BBB Morphology and Width after CRT-D
Outcomes Among 24,169 Medicare Beneficiaries

All-Cause Mortality by QRS Morphology and Width

All-Cause Readmission by QRS Morphology and Width

Peterson et al. JAMA 2013.
CRT in Narrow QRS

A Primary Composite Outcome

Patients with Event (%) vs Years since Randomization

- CRT
- Control

P=0.15

No. at Risk
CRT 404 297 223 155 103 65 42 19
Control 405 302 236 166 119 71 44 15

B Death from Any Cause

Patients with Event (%) vs Years since Randomization

- CRT
- Control

P=0.02

No. at Risk
CRT 404 334 267 199 132 84 56 25
Control 405 335 269 195 141 87 62 27

Ruschitzka et al. NEJM 2013
Resynchronization Therapy
Electrical Fix For a Complex Problem

Truong QA, et al; Critical Pathways in Cardiology 2008
Traditionally, LV leads are placed by anatomic criteria on the lateral wall of the left ventricle.

More recent studies have not supported solely using anatomic guidance, other than avoiding the apex.

However, recent studies have shown the importance of physiologic guidance of lead placement.
LV Lead Position & Clinical Outcome
Death &/or Heart Failure

- No difference amongst Anterior, Posterior and Lateral lead positions
- Apical lead positions associated with a significantly worse clinical outcome
- Differences maintained even after non-apical leads sub-stratified into mid-ventricular and basal
REVERSE LV Lead Analysis: Apical vs Non-Apical

Hazard ratio, 3.74 (CI, 1.60-8.73)

P = 0.0011

Death or HF Hospitalization (%)

Time since randomization (days)

No. at Risk
Non-Apical: 246 242 115 111 2
Apical: 39 37 11 9 1

C Thébault et Al  Eur Heart J 2012
REVERSE: LV lateral vs LV Non-lateral

Hazard ratio, 0.44 (CI, 0.19-0.99)
P = 0.041

No. at Risk
Non-Lateral  56  55  30  25  1
Lateral 229 224 96 95 2
Imaging Guided LV Lead Positioning

TARGET & STARTER

**TARGET:** Khan *JACC* 59:1509, 2012
- RCT of 220 CRT pts
  - Control: post-lat / lat CS branch
  - Targeted: 2D echo speckle-tracking: latest activated segment
- LV pacing concordance
  - Control: 47%
  - Targeted: 63%

**STARTER:** Saba *Circ HF* 6:427, 2013
- RCT of 187 CRT pts
- Also used speckle-tracking ECHO
- LV pacing concordance
  - Control: 66%
  - Targeted: 85%
Physiologic Guided Lead Positioning: QLV Interval Measurement

Example 1:

- Lead II
- Atrial EGM
- Right V EGM
- Left V EGM

Example 2:

- Lead II
- Atrial EGM
- Right V EGM
- Left V EGM

QLV Interval Measurement:

- Example 1: QLV Interval 90 ms
- Example 2: QLV Interval 165 ms
Q-LV Interval to Predict Acute Response

Gold et al, J Cardiovasc Electrophysiol 2014
Impact of QLV on Reverse and QOL with CRT

Gold et al, Eur Heart J. 2011

Data presented as median ± inter-quartile range
QLV and Reduction in MR at 6 Months

Longer QLV associated with ↓ MR at 6 months

Most leads were placed in the anterolateral or posterolateral veins, as reported by the implanting physicians.

- Mid-anterolateral (n=89): QLV range = 10 – 195 ms
- Mid-posterolateral (n=230): QLV range = 15 – 195 ms
Interventricular Conduction Delay

- The electrical time between RV and LV leads is a surrogate for QLV (LV delay)
- It measures the electrical resynchronization that will occur with biventricular stimulation
- It is a simple measure that can be manually or automatically measured by devices
Interventricular Electrical Delay

Example 1
- Lead II
- Atrial EGM
- Right V EGM
- Left V EGM

Example 2
- Lead II
- Atrial EGM
- Right V EGM
- Left V EGM

Q:
- RV
- LV

50 ms
55 ms
100 ms
Association of RV-LV Time with LV Remodeling and QOL

- **LVESV**
  - Change in LVESV (ml)
  - Kruskal-Wallis test, $P < 0.001$

- **LVEDV**
  - Change in LVEDV (ml)
  - Kruskal-Wallis test, $P < 0.001$

- **LVEF**
  - Change in LVEF (%)
  - Kruskal-Wallis test, $P < 0.001$

- **Quality of Life**
  - Change in QOL (points)
  - Kruskal-Wallis test, $P = 0.024$
RV-LV Time: SMART AV

![Graph showing death or HFH risk factors](image)

- **Overall**: 1342, HR 0.62, P-value 0.002
- **LBBB**: 908, HR 0.63, P-value 0.011
- **Non-LBBB**: 434, HR 0.61, P-value 0.119
- **QRS >= 150 ms**: 859, HR 0.53, P-value 0.001
- **QRS < 150 ms**: 483, HR 0.94, P-value 0.780
- **CAD**: 802, HR 0.66, P-value 0.025
- **No CAD**: 802, HR 0.66, P-value 1.000
- **Male**: 890, HR 0.82, P-value 0.254
- **Female**: 452, HR 0.37, P-value 0.001
- **NYHA Class IV**: 75, HR 0.88, P-value 0.803
- **NYHA Class II/III**: 1267, HR 0.62, P-value 0.002
- **Age > 65 years**: 820, HR 0.62, P-value 0.009
- **Age <= 65 years**: 522, HR 0.64, P-value 0.081
- **LVEF > 25%**: 423, HR 0.68, P-value 0.179
- **LVEF <= 25%**: 913, HR 0.59, P-value 0.003

*Favors RV-LV >= 70 ms, Favors RV-LV < 70 ms*
RV-LV Time and Clinical Outcome: PEGASUS

Log-rank p = 0.002
## Importance of CRT Outcome

### Patient selection

<table>
<thead>
<tr>
<th>Pacing site</th>
<th>Right</th>
<th>Wrong</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Wrong</td>
<td>+ / -</td>
<td>-</td>
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</table>

Same considerations for devices optimization
LVESV Response by Subgroup

Univariate Logistic Regression Results

Favors Shorter QLV  Favors Longer QLV  OR [95% CI]

All Patients  2.61 [1.77, 3.87]

LBBB  2.34 [1.49, 3.68]
RBBB  2.12 [0.51, 8.91]
Other IVCD  1.92 [0.52, 7.18]

QRS<=150  2.39 [1.36, 4.21]
QRS>150  2.89 [1.48, 5.65]

Ischemic  2.75 [1.63, 4.64]
Non-ischemic  1.93 [1.03, 3.60]

Male  2.25 [1.39, 3.65]
Female  2.82 [1.40, 5.69]
FREEDOM Trial Results: Primary Endpoint
HF Clinical Composite Score
(Intent-to-Treat Analysis)

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
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<td>HF CCS</td>
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<td>Improved</td>
<td>551</td>
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<td>Worsened</td>
<td>189</td>
<td>23.16</td>
<td></td>
<td>183</td>
<td>22.10</td>
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<tr>
<td>Total</td>
<td>816</td>
<td>100</td>
<td></td>
<td>828</td>
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No treatment differences in pre-specified ischemic and non-ischemic sub groups
Primary Endpoint - LVESV

<table>
<thead>
<tr>
<th>Group</th>
<th>Change in Volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smart Delay</td>
<td>-25 (n = 283)</td>
</tr>
<tr>
<td>Echo</td>
<td>-20 (n = 282)</td>
</tr>
<tr>
<td>Fixed</td>
<td>-15 (n = 281)</td>
</tr>
</tbody>
</table>
ADAPTIVE CRT

Non-inferiority P = 0.0007

- Improved: 73.6% (aCRT n=318), 72.5% (Echo n=160)
- Unchanged: 12.3% (aCRT), 16.3% (Echo)
- Worsened: 14.2% (aCRT), 11.3% (Echo)

Martin et al Heart Rhythm 2012
CLEAR: Primary Endpoint

Clinical response rate to CRT (composite criterion)

<table>
<thead>
<tr>
<th>Response rate (%)</th>
<th>SonR group (n=87)</th>
<th>Control group (n=99)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>78%</td>
<td>62%</td>
<td>0.015</td>
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*Composite criterion including NYHA functional class, death from any cause, deaths and hospitalizations for management of HF, and QOL

<table>
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<th>Endpoint</th>
<th>SonR group</th>
<th>Control group</th>
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<tr>
<td>Free from deaths / HF hospitalizations</td>
<td>84%</td>
<td>75%</td>
<td>0.13</td>
</tr>
<tr>
<td>NYHA class decrease</td>
<td>81%</td>
<td>64%</td>
<td>0.0064</td>
</tr>
<tr>
<td>QOL score increase</td>
<td>74%</td>
<td>65%</td>
<td>0.19</td>
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Are We Thinking About AV Optimization Wrong?

- We can not always turn lemons into lemonade! A nonresponder may be a nonresponder (narrow QRS, scar, lead position)

- However, optimal pacing may maximize a positive response
Changes in LVESV as a function of QLV and AV optimization

The graph shows the change in LVESV (as a percentage change) for different QLV intervals (0-70ms, 70-95ms, 95-120ms, 120-195ms) with and without AV optimization. For each QLV interval, the number of subjects is indicated (N=35, N=46, N=37, N=30, N=35, N=34, N=30, N=33). The change in LVESV is given as a percentage change from baseline.

- For QLV: 0-70ms, the change in LVESV is -10% for Fixed and -7% for SmartDelay, with P=NS.
- For QLV: 70-95ms, the change in LVESV is -10% for Fixed and -20% for SmartDelay, with P=NS.
- For QLV: 95-120ms, the change in LVESV is -23% for Fixed and -27% for SmartDelay, with P=NS.
- For QLV: 120-195ms, the change in LVESV is -23% for Fixed and -47% for SmartDelay, with P=0.05.

The results suggest that SmartDelay optimization leads to a greater decrease in LVESV compared to Fixed optimization, especially for longer QLV intervals.
Adaptive LV Pacing Subgroup Analysis

Patients with Higher Percentage Synchronized LV Pacing in the aCRT Arm had a lower rate of death and HF hospitalizations

Logrank
P = 0.003

Birnie D. et al., Heart Rhythm 2013.
PEGASUS: HF Hospitalization or Death

![Graph showing HF-free survival over months with Log-rank p = 0.002 and comparison between two groups with >= 67 ms and < 67 ms.]
Impact of BiV pacing % on Survival with CRT

Hayes et al, Heart Rhythm 2011
Consider Reversible Causes

Non-responder

Atrial Fibrillation
- Maintain NSR
- Rate control (AVN vs. MED)
- Adjust upper pacing rate
- Program VVIR/VS Response
- Individualize strategy (LV)

Volume Status

Cardiac Ischemia
- Rule out ischemia
- Treat ischemia

Other Co-morbidities
- Depression
- COPD
- Arthritis
- Anemia etc.
Evaluation of Non-responder

• Is it an inappropriate candidate
  – Consider a trial of no CRT

• Assess for reversible and treatable causes
  – Lead dislodgement
  – Loss of capture
  – Atrial fibrillation
  – Metabolic or medical issues exacerbating HF
  – Low LV pacing percentage

• Consider interventions to improve CRT response
  – Optimize medical regimen
  – Programming AV delays or rate to improve LV pacing
  – Invasive lead reposition or additions
The Initial Evaluation

NON-RESPONDER

CXR

Device Interrogation

ECG

Lateral Wall (Mid-Ventricular)

Dislodged into CS
CRT Follow-Up Clinic

Hazard ratio, 0.62 (95% CI 0.47-0.84) p=0.0015 by stratified log-rank test

Multi-Disciplinary CRT Clinic

Conventional Follow-Up

Patients at risk
Convent. FU 173 120 98 81 69
CRT Clinic 255 208 162 119 85

Time [months]

Altman R / Singh JP et al, AHA 2011
Summary

• There are many definitions of CRT response with no consensus on the best choice
• In practice, non-responders are classified by subjective assessment. However, given the placebo effect of device implantation this should be supplemented with some objective criteria such as exercise or echo response
• A systematic approach to the evaluation and treatment of nonresponders is vital, including device evaluation, HF status and noncardiac contributing causes
• Multidisciplinary clinics can reduce nonresponder rates
Electrical Targeting in non-LBBB Clinical & Echocardiographic outcome

- Intra-procedural left ventricular lead electrical delay LVLED in non-LBBB a determinant of outcome
- Graded remodeling response

Kandala J et al. European Heart Journal 2013
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CRT Response Evaluation

**Clinical Evaluation**
Improvement in symptoms and signs of heart failure

- Important Considerations:
  - Assess NYHA class
  - Functional capacity
  - 6MW, VO2
  - Quality of Life
  - Adjust medical therapy
    - Lower diuretic dose, optimise BB dose

**Evaluation of LV function**
Improvements in LV dimensions, LVEF and mitral regurgitation

- Assess
  - LV function by Doppler Echo
  - BNP/NT proBNP

**Device Evaluation**
Ascertain % biventricular pacing

- Consider documentation in file of % biventricular pacing:
  - Heart rate histograms
  - Improvements in HRV, activity/day
  - Arrhythmia burden
Clinical Case

- 68 y/o woman, DCM, NYHA III
- Medications: Carvedilol, lisinopril, spironolactone, furosemide
- ECG: LBBB (QRS 162 msec, PR 208 msec)
- LVEF: 25%, LVEDD: 66 mm

The perfect CRT-D candidate!
In which vein to Implant?
Which targeted position?
Pragmatic consideration: lead stability
BiV pacing
BiV pacing
REVERSE

HR (95%CI): 0.38 (0.20-0.73)  
P=0.003

Number at Risk
CRT OFF  82  79  76  70  39
CRT ON   180 176 173 168  77

Daubert C. J Am Coll Cardiol. 2009;54(20):1837-1846