Non-responders to CRT: what is wrong in this patients?

Angelo Auricchio, MD FESC
Director, Cardiac Electrophysiology Programme, Fondazione Cardiocentro Ticino, Lugano, Switzerland
Professor of Cardiology, University of Magdeburg, Germany
President European Heart Rhythm Association
In the era of CRT, heart failure is a curable disease!

### History

- 72 yrs old lady
- Parox atrial fibrillation, LBBB, QRS 175 ms
- Moderate hypertension
- Sleep apnea
- Moderate renal failure

- 1st diagnosis HF in 1995
  - No coronary artery disease
  - Optimal drug therapy

- Recurrent episodes of HF decompensation
  - Progressive intolerance to heart failure medication

- CRT-D implantation in 2001

2012: NYHA Class I
Follow-up by home doctor and remotely
No episode of atrial fibrillation since 2001
The phenotype of CRT super-responder

Hypo-responders: Δ LVEF < 7.9% (25%)
Responders: Δ LVEF 8% – 14.4% (49%)
Super-responders: Δ LVEF > 14.4% (25%)

Unadjusted P < 0.001

Table 3: Multivariate Analysis of Predictors of LVEF Super-Response

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1.96</td>
<td>1.32–2.90</td>
<td>0.001</td>
</tr>
<tr>
<td>QRS duration ≥ 150 ms</td>
<td>1.79</td>
<td>1.17–2.73</td>
<td>0.007</td>
</tr>
<tr>
<td>LBBB</td>
<td>2.05</td>
<td>1.24–3.40</td>
<td>0.006</td>
</tr>
<tr>
<td>Body mass index &lt; 30 kg/m²</td>
<td>1.51</td>
<td>1.03–2.20</td>
<td>0.035</td>
</tr>
<tr>
<td>No prior myocardial infarction</td>
<td>1.80</td>
<td>1.20–2.71</td>
<td>0.005</td>
</tr>
<tr>
<td>Left atrial volume index, SD*</td>
<td>1.47</td>
<td>1.21–1.79</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Per 1-U SD below mean.
# ESC Clinical Practice Guidelines - 2012

## NYHA Class III-IV

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LBBB QRS morphology</strong></td>
<td>I</td>
<td>A</td>
<td>156, 157</td>
</tr>
<tr>
<td>CRT-P/CRT-D is recommended in patients in sinus rhythm with a QRS duration of ≥120 ms, LBBB QRS morphology, and an EF ≤35%, who are expected to survive with good functional status for &gt;1 year, to reduce the risk of HF hospitalization and the risk of premature death.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-LBBB QRS morphology</strong></td>
<td>IIa</td>
<td>A</td>
<td>156, 157</td>
</tr>
<tr>
<td>CRT-P/CRT-D should be considered in patients in sinus rhythm with a QRS duration of ≥150 ms, irrespective of QRS morphology, and an EF ≤35%, who are expected to survive with good functional status for &gt;1 year, to reduce the risk of HF hospitalization and the risk of premature death.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## NYHA Class II

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LBBB QRS morphology</strong></td>
<td>I</td>
<td>A</td>
<td>154, 155</td>
</tr>
<tr>
<td>CRT, preferably CRT-D is recommended in patients in sinus rhythm with a QRS duration of ≥130 ms, LBBB QRS morphology, and an EF ≤30%, who are expected to survive for &gt;1 year with good functional status, to reduce the risk of HF hospitalization and the risk of premature death.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-LBBB QRS morphology</strong></td>
<td>IIa</td>
<td>A</td>
<td>154, 155</td>
</tr>
<tr>
<td>CRT, preferably CRT-D should be considered in patients in sinus rhythm with a QRS duration of ≥150 ms, irrespective of QRS morphology, and an EF ≤30%, who are expected to survive for &gt;1 year with good functional status, to reduce the risk of HF hospitalization and the risk of premature death.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[www.escardio.org](http://www.escardio.org)
In the era of CRT, heart failure is still a challenging disease!

History

56 yrs old gentleman
Parox atrial fibrillation, IVCD, QRS 140 ms
Sleep apnea
Moderate renal failure

- 1st diagnosis HF in 2001
  - PTCA LAD
  - Optimal drug therapy
  - Reduced ejection fraction (LVEF 25%)
  - ICD implantation for primary prevention of SCD in 2002
- Recurrent episodes of HF decompensation
  - Upgrade of ICD to CRT-D in 2005
  - Ablation of paroxysmal atrial fibrillation in 2007
- Frequent hospitalization due to HF decompensation
  - Implantation of MitraClip in 2010
- Persistent symptoms of HF (NYHA class III)
  - Implantation of WiCS system in 2011

NYHA Class II, HF out-patient clinic
In the era of CRT, heart failure is still a challenging disease!

What was wrong in this case?

1) Disease progression
2) Suboptimal therapy delivery
3) Inability to match proper therapy with substrate / disease
4) Multiple mechanisms contributing to heart failure
The puzzle of response (or non-response) to CRT

Strategies to recompose the puzzle
The binary category approach: Outcome varies according to measurement method.

Daubert JC et al Europace 2012
The multiple categories of response are indicating different treatment strategy goals post-CRT

Unadjusted

P<0.001

Convert a hypo-responder into a responder

Maximize the response

Hsu et al JACC 2012
The multiple categories of response by Seattle Heart Failure Score

- 3% per year mortality rate
- 6% per year mortality rate
- 12% per year mortality rate
Multidisciplinary management

Integrated clinic setting by a team of subspecialists from the:
- heart failure
- electrophysiology, and
- echocardiography service
at 1-, 3-, and 6-months post-implant

Conventional care setting, patients were seen as needed by each subspecialist and in EP device clinic in separate visits at varying intervals. Echocardiogram-guided optimizations were dictated by physician discretion and not performed routinely.

Using binary category of response to CRT w/out consideration on remote device/arrhythmia management

Altman et al. Eur Heart J 2012
Causes of no-response to CRT in the era of binary category assessment

Mullens W et al. JACC 2009;53:765–73
**Conclusions**—Neither SmartDelay nor echocardiography was superior to a fixed AV delay of 120 milliseconds. The routine use of AV optimization techniques assessed in this trial is not warranted. However, these data do not exclude possible utility in selected patients who do not respond to cardiac resynchronization therapy.
Suboptimal AV Delay as cause of no-response to CRT

Mullens W et al. JACC 2009;53:765–73
Causes of no-response to CRT

- Suboptimal AV Timing
- Arrhythmia
- Anemia
- Suboptimal LV Lead Position
- < 90% Biventricular Pacing
- Suboptimal Medical Therapy
- Persistent Mechanical Dyssynchrony
- Underlying narrow QRS
- Compliance Issues
- Primary RV Dysfunction

Mullens W et al. JACC 2009;53:765–73
CRT and the relationship of percent BiV pacing to symptoms and survival

36,935 pts followed up in the LATITUDE RM network

BiV ≥99.6% = 24% reduction in mortality
BiV ≤94.8% = 19% increase in mortality
Reasons for loss of CRT

32,844 Patients

In pts with permanent AF and HF, using data from CRT counters alone to estimate percentage of BiV stimulation time may be MISLEADING, because counters likely overestimate the degree of BiV pacing.
Frequent VES as cause of no-response to CRT
Causes of no-response to CRT

- Suboptimal AV Timing
- Arrhythmia
- Anemia
- Suboptimal LV Lead Position
- < 90% Biventricular Pacing
- Suboptimal Medical Therapy
- Persistent Mechanical Dyssynchrony
- Underlying narrow QRS
- Compliance Issues
- Primary RV Dysfunction
Importance of LV lead location in chronic canine model of myocardial infarction

- LBBB
- LBBB+LADi
- LBBB+LCXi

**Resynchronization**

**LVdP/dtmax**

**Stroke work**
Outcome: pacing in scar vs. outside scar

Biophysical Modeling to Simulate the Response to Multisite Left Ventricular Stimulation Using a Quadripolar Pacing Lead

Niederer et al. PACE 2012
Causes of no-response to CRT

- Suboptimal AV Timing
- Arrhythmia
- Anemia
- Suboptimal LV Lead Position
- < 90% Biventricular Pacing
- Suboptimal Medical Therapy
- Persistent Mechanical Dyssynchrony
- Underlying narrow QRS
- Compliance Issues
- Primary RV Dysfunction

Mullens W et al. JACC 2009;53:765–73
CRT-D has neutral effect in pts with RBBB, but in those with ICVD …..
LV activation sequence (U-shaped) in dilated cardiomyopathy and heart failure

Normal QRS Morphology and Duration

- QRS Duration: 125 ms
- QRS Duration: 158 ms
Local EGMs in complete LBBB

Unipolar EGM (NOGA)

Unipolar EGM (NOGA)

Auricchio et al. Circulation 2004
Changes of line of block position and length with QRS change in LBBB patients

Appearance of Line of Block (Basal region)

Lengthening and anterior displacement

Normal QRS

QRS 120 – 140 ms

QRS >140
The use of speckle-tracking echocardiography to the target LV lead placement yields significantly improved response and clinical status and lower rates of combined death and heart failure–related hospitalization.
CRT-D has neutral effect in pts with RBBB, but why so?
Importance of radial dyssynchrony on outcome

Hara et al. Eur Heart J 2012
Is CRT delivery suboptimal in RBBB patients?
CRT in a RBBB Patient

Pre-Implantation

1-yr after CRT

LAO 45°
Causes of no-response to CRT

- Suboptimal AV Timing
- Arrhythmia
- Anemia
- Suboptimal LV Lead Position
- < 90% Biventricular Pacing
- Mitral valve disease
- Suboptimal Medical Therapy
- Persistent Mechanical Dyssynchrony
- Underlying narrow QRS
- Compliance Issues
- Primary RV Dysfunction

Mullens W et al. JACC 2009;53:765–73
**Age**  70.3 ± 9.2 yrs

**Male Gender**  44 (86%)

**Ischemic cardiomyopathy**  37 (73%)

**Previous interventions (%)**  
- CABG or PCI  24 (47%)
- Valve surgery  4 (8%)

**Functional New York Heart Association Class**  
- III  32 (63%)
- IV  17 (35%)

**CRT-D (%)**  47 (92%)

**Month since CRT**  32.9 ± 25.7
Change in NYHA class and MR after MitraClip in 51 CRT non-responders

Auricchio et al. JACC 2011; 58: 2183-9
Reverse remodeling in CRT non-responders treated by MitraClip

A. Auricchio et al. JACC 2011; 58: 2183-9
Conclusions

A multidisciplinary protocol-driven approach to ambulatory CRT patients who did not exhibit a positive response long after implant may uncover potential contributors to a suboptimal response such as

- Suboptimal AV Delay
- Frequent atrial and/or ventricular arrhythmias
- Major valvular abnormalities
- Pacing in scar dense areas
- Mismatch between pacing and electrical / mechanical abnormality

may potentially maximize the potential of CRT, and

may be associated with a reduction in adverse events.