CRT response: definition and handling of non-responders

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Definition of non-responders

First of all definition of responders
Chronic heart failure and CRT
What are we talking about?

Heart failure is a **COMPLEX MULTIFACTORIAL** constantly mutating and **PROGRESSIVE** disease...

What does it mean to **RESPOND** to CRT?

1) → To **STOP** the evolution of the disease?

2) → To obtain a **PARTIAL** recovery?

3) → To obtain a **COMPLETE** recovery (i.e. a remission of the disease?)
<table>
<thead>
<tr>
<th>HEART FAILURE</th>
<th>RESPONDERS</th>
<th>NON-RESPONDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive disease</td>
<td>Stop progression, Clinical stability</td>
<td>Stop progression, Clinical instability</td>
</tr>
<tr>
<td>Impaired exercise tolerance</td>
<td>↑ VO2/6MWT, ↓ QOL</td>
<td>So... Easy task?</td>
</tr>
<tr>
<td>Drug-refractory</td>
<td>↑↑ Drug (βblock-ACE inh)</td>
<td>unchanged Drugs</td>
</tr>
<tr>
<td>Impaired LV function</td>
<td>↑ LV EF, ↓ MR, ↓ LV ESV</td>
<td>Unchanged worsened LVEF, LV ESV, MR</td>
</tr>
<tr>
<td>High hosp rate</td>
<td>↓ Hosp rate</td>
<td>unchanged/wors Hosp</td>
</tr>
<tr>
<td>High mortality rate</td>
<td>↓ Mortality rate</td>
<td>unchanged/wors Mort</td>
</tr>
</tbody>
</table>
CRT response: definition of non-responders

“response is itself an incorrect dichotomy

→ Can we neatly divide HF pts into responders and non-responders?!

→ there will be a spectrum of response (ranging from harm to “miracle”) like all medical therapies

CRT modify

Symptoms

More importante and clear from pt’s perspective

Echo

Very appreciated by EP and HF specialists

Outcome

Not always associated to echo and symptoms
Variable CRT RESPONSE

criteria

1995

Acute hemodynamic benefit

Symptomatic improvement

LV function improvement

Improved survival

↑ Systolic BP, ↓ PWP, aortic PP, ↑ dp/dt

↑ VO2/ 6MWT, ↓ QOL, ↓ NYHA class

↑ LV EF, ↓ MR ↓ LV ESV

Better overall survival

" survival for HF death

2011
Response criteria

Echocardiographic

1. \( \uparrow \text{LVEF} \geq 5\% \) (absolute)\(^{1,2} \)
2. \( \uparrow \text{LVEF} \geq 15\% \)\(^{3,4} \)
3. \( \downarrow \text{LVESV} \geq 10\% \) and did not die of progressive HF within 6 months\(^{20,27} \)
4. \( \downarrow \text{LVESV} > 15\% \)\(^{2,5-10} \)
5. \( \text{LVESV} < 115\% \) of baseline\(^{26} \)
6. \( \downarrow \text{LVESV}I > 15\% \)\(^{25} \)
7. \( \downarrow \text{LVEDV} > 15\% \)\(^{2} \)
8. \( \uparrow \text{Stroke volume} \geq 15\% \)\(^{4,21,22} \)

Clinical

\( \downarrow \text{NYHA} \geq 1 \)
\( \downarrow \text{NYHA} \geq 1, \text{no HF death} \)
\( \downarrow \text{NYHA} \geq 1 \) and \( \uparrow \text{6MWD} \geq 25\% \)
\( \downarrow \text{NYHA} \geq 1 \) and \( \uparrow \text{6MWD} \geq 25\%, \text{no HF death} \)

\( \uparrow \text{6MWD} \geq 10\%, \text{no HF death, no transplant} \)

Two of the following 3: \( \downarrow \text{NYHA} \geq 1, \uparrow \text{6MWD} \geq 50 \text{ m}, \downarrow \text{QOL} \geq 15 \)

Clinical composite score improved

Combined

\( \uparrow \text{LVEF} > 5 \text{ units or } \uparrow \text{6MWD} \geq 50 \text{ m and} \)
\( \downarrow \text{NYHA} \geq 1 \) or \( \downarrow \text{QOL} \geq 10 \)

Brandon K. Fornwalt, PhD;
(Circulation. 2010;121:1985-1991.)
Agreement is poor among current criteria used to define response to cardiac resynchronization therapy.

Brandon K. Fornwalt, PhD; William W. Sprague, BS; Patrick BeDell, BBA, RDCS; Jonathan D. Suever, BS; Bart Gerritse, PhD; John D. Merlino, MD; Derek A. Fyfe, MD, PhD; Angel R. León, MD; John N. Oshinski, PhD

(Circulation. 2010;121:1985-1991.)
Variable CRT RESPONSE criteria in current literature (II)

Which one should be utilized in clinical practice?

<table>
<thead>
<tr>
<th>Response Criteria</th>
<th>Response Rate, %</th>
<th>No. Evaluable (% of Total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiographic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ LVEF &gt;5 units</td>
<td>51</td>
<td>286 (67)</td>
</tr>
<tr>
<td>↑ LVEF &gt;15% (relative)</td>
<td>54</td>
<td>286 (67)</td>
</tr>
<tr>
<td>↓ LVESV ≥10%, no HF death</td>
<td>62</td>
<td>291 (68)</td>
</tr>
<tr>
<td>↓ LVESV &gt;15%</td>
<td>56</td>
<td>286 (67)</td>
</tr>
<tr>
<td>LVESV &lt;115% of baseline</td>
<td>91</td>
<td>286 (67)</td>
</tr>
<tr>
<td>↓ LVEDV &gt;15%</td>
<td>49</td>
<td>286 (67)</td>
</tr>
<tr>
<td>↑ Stroke volume ≥15%</td>
<td>34</td>
<td>286 (67)</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ NYHA ≥1</td>
<td>71</td>
<td>385 (90)</td>
</tr>
<tr>
<td>↓ NYHA ≥1, no HF death</td>
<td>70</td>
<td>390 (92)</td>
</tr>
<tr>
<td>↓ NYHA ≥1 and ↑ 6MWD ≥25%</td>
<td>33</td>
<td>348 (82)</td>
</tr>
<tr>
<td>↓ NYHA ≥1 and ↑ 6MWD ≥25%, no HF death</td>
<td>32</td>
<td>353 (83)</td>
</tr>
<tr>
<td>↑ 6MWD ≥10%, no HF death, no transplant</td>
<td>61</td>
<td>353 (83)</td>
</tr>
<tr>
<td>Two of the following: ↓ NYHA ≥1, ↑ 6MWD ≥50 m, ↓ QOL ≥15</td>
<td>63</td>
<td>339 (80)</td>
</tr>
<tr>
<td>Clinical composite score improved</td>
<td>69</td>
<td>426 (100)</td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ LVEF &gt;5 units or ↑ 6MWD ≥50 m and</td>
<td>71</td>
<td>250 (59)</td>
</tr>
<tr>
<td>↓ NYHA ≥1 or ↓ QOL ≥10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

**Echo**

Easy, not expensive, reproducible
Consensual evaluation of dyssynchrony (?!)

**Clinical criteria**

→ Sometimes difficult/inaccurate evaluation
→ QOL sensible to comorbidities
→ limited usefulness/nonsense in early stage of the disease
Sometimes the pure (…poor) EP specialist may think that …

Inter-ventricular dyssynchrony criteria

Intra-ventricular dyssynchrony criteria

Are like a Babel tower……

In fact.. Prospect trial

Results of the Predictors of Response to CRT (PROSPECT) Trial

Eugene S. Chung, MD; Angel R. Leon, MD; Luigi Tavazzi, MD; Jing-Ping Sun, MD; Petros Nihoyannopoulos, MD; John Merlino, MD; William T. Abraham, MD; Stefano Ghio, MD; Christophe Leclercq, MD; Jeroen J. Bax, MD; Cheuk-Man Yu, MD, FRCP; John Gorcsan III, MD; Martin St John Sutton, FRCP; Johan De Sutter, MD PhD; Jaime Murillo MD

Conclusion—Given the modest sensitivity and specificity in this multicenter setting despite training and central analysis, no single echocardiographic measure of dyssynchrony may be recommended.
The Role of Echocardiography in Predicting Responders to Cardiac Resynchronization Therapy
– Results From the Japan Cardiac Resynchronization Therapy Registry Trial (J-CRT) –

Yoshihiro Seo, MD; Hiroshi Ito, MD; Satoshi Nakatani, MD; Mitsuaki Takami, MD; Shigeto Naito, MD; Tsuyoshi Shiga, MD; Kenji Ando, MD; Yuji Wakayama, MD; Kazutaka Aonuma, MD; the J-CRT investigators

Conclusions: Echocardiographic parameters did not show significant power to detect CRT responders independently. (Circ J 2011; 75: 1156–1163)
Selecting Patients for Cardiac Resynchronization Therapy

The Fallacy of Echocardiographic Dyssynchrony

✓ “sophisticated methodics”: no short nor long term reproducibility, no meaningful predictive value, intra and interobserver variability, not validated in RCT with robust clinical end points

This is why until now no dyssynchrony criteria is included in CRT Guidelines...
Assessing non-response with echocardiogram

Is there a simple, cheap way...?

Properly using some **simple** TT echo informations !!!:

Simple but potentially valuable data to identify non responders:

- **EF extremely low (< 15-18%)**
- **EDV > 250 ml** [Gasparini AHA 2003]
- Large miocardial scars/ poor LV viability
- **End-diastolic wall thickness (EDWT) < 6 mm** [Cwajg et al, JACC 2000]
- Assumed that moderate as opposed to severe LV dilatation are more likely to respond to CRT ... [Auricchio et al, JACC 2002, Gasparini et al, PACE 2007]
Assessing non-response with echo/NMR

Viable myocardium

Non-viable myocardium

Echo-dobutamine

Unlikely to benefit from CRT !!!

"Cardboard"
After the lack of definitive response criteria... it should be remembered that...

Failing to achieve specific “response” criteria is NOT necessarily “non response”

Without CRT a pt
- → may have undergone further adverse remodeling
- → had more limited exercise tolerance
- → ...or even be dead

“non responder” → death for HF
- → unchanged/worse NYHA
- → no LVESV↓, no LVEF ↑
- → unchanged/worse QOL
Iperresponders (HF remission)

Alive CRT pts

Non responders

Poor responders (weak improvement)

Unchanged

Worsened

Remission of left ventricular systolic dysfunction and of heart failure symptoms after cardiac resynchronization therapy: Temporal pattern and clinical predictors

Maurizio Gasparini, MD, François Regoli, MD, PhD, Carlo Ceriotti, MD, Paola Galimberti, MD, Renato Bragato, MD, Stefano De Vita, MD, Daniela Pini, MD, Bruno Andreuzzi, MD, Maurizio Mangiavacchi, MD, and Catherine Klersy, MD

(Am Heart J 2008;155:507-14.)

↑ EF < 5% ; ↓ LVESV <10% ; = NYHA )
40 pts with CRT implanted > 3 months admitted for acute heart failure → i.e. NON RESPONDER!

Are these patients non responders?! Real non responder!

Only 2 out of 40 non responder for ↓ wedge with CRT-off

No one out of 40, ↑ CO or SBP with CRT-off!
“A significant worsening of hemodynamics was observed immediately when CRT was programmed OFF”....

Could we continue to consider this patient as a non responder to CRT ?!
**Responders**  
\[ \uparrow EF < 5-10\% \]

**Iperresponders**  
\[ EF > 50\% \]

**Poor responders**  
\[ \uparrow EF < 1-5\% \]

**Non responders**

**Dramatic worsening**

- Unchanged
  - CRT OFF
  - Unchanged / Better
  - Absolutely TRUE NON RESPONDERS

- Worsened
  - CRT OFF
  - Worsened
  - Unchanged / Better

- Unchanged
  - CRT OFF
  - Unchanged / Better
  - Absolutely TRUE NON RESPONDERS

- Worsened
  - CRT OFF
  - Worsened
  - Unchanged / Better

- Unchanged
  - CRT OFF
  - Unchanged / Better
  - Absolutely TRUE NON RESPONDERS
The real “non responder” is the patient with absolutely NO CHANGE or (even if extremely rare) with clinical and echo AMELIORATION when CRT device is switched OFF.
Handling of non-responders
Non-responders

“inappropriate” enrollment

Correctable causes of non response

Irreversible path of disease progression

Too early
(longer f.u needed in early stage of HF)

No chances

Otx, LVAD, mitral clip, cardiac surgery
Try to favour LV filling by atrial sensing (ie DDD 40 programming if no documented atrial disease).

Always check for AV/VV programming (echo guided!)

Always treat ventricular arrhythmias / or atrial arrhythmias (drugs/ablation…)

Evaluate LV repositioning different/adjunctive LV lead

Septal RV lead


If BV < 95% In AF AVJ ablation should be performed

In VEB, NSVT, amiodarone…

Always check for maximal dosage of β-block/Ace-inh

Potential reasons for suboptimal response

Always check for maximal dosage of β-block/Ace-inh

Suboptimal AV Timing Arrhythmia Anemia

Suboptimal LV Lead Position Elevation Pace

In AF AVJ ablation should be performed

In VEB, NSVT, amiodarone…
At 6-min-WT loss of BIV pacing
Always check for anodic capture

1st CS lead Oct 2008

Connected with a Y adapter

2nd CS lead in PL vein March 2009
Potential reasons for suboptimal response

The 2 most important

<table>
<thead>
<tr>
<th>Reason</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suboptimal AV Timing</td>
<td>45%</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>35%</td>
</tr>
<tr>
<td>Anemia</td>
<td>25%</td>
</tr>
<tr>
<td>Suboptimal LV Lead Position</td>
<td>20%</td>
</tr>
<tr>
<td>&lt; 90% Biventricular Pacing</td>
<td>15%</td>
</tr>
<tr>
<td>Suboptimal Medical Therapy</td>
<td>10%</td>
</tr>
</tbody>
</table>
Four-Year Efficacy of Cardiac Resynchronization Therapy on Exercise Tolerance and Disease Progression
The Importance of Performing Atrioventricular Junction Ablation in Patients With Atrial Fibrillation
Maurizio Gasparini, MD,*, Angelo Aurichio, MD, PhD,‡§ François Regoli, MD,* Cecilia Fantoni, MD,‡ Mihoko Kawabata, MD,‡ Paola Galimberti, MD,* Daniela Pini, MD,* Carlo Ceriotti, MD,* Edoardo Gronda, MD,* Catherine Klersy, MD, MSc,† Simona Fratini, MD,‡ Helmut H. Klein, MD‡

* Milan and Pavia, Italy; ‡ Magdeburg, Germany; and § Lugano, Switzerland

673 pts

162 Permanent AF

BVP % at 2 months

≤85%

→ 85%

114 pts

AF-abl

48 pts

Drugs + VRR

J Am Coll Cardiol 2006; 48 (4): 734–743

Growing BIV % required !!!!!

Mean F.U.: 25.2 ± 18 months
1) Significant EF increase both in SR and AF-abl. No change for AF drugs.

2) Functional capacity score increase both in SR and AF-abl.

3) Similar LVESV reductions in SR and AF-abl.
Heart Failure Decompensation and All-Cause Mortality in Relation to Percent Biventricular Pacing in Patients With Heart Failure

Is a Goal of 100% Biventricular Pacing Necessary?

Bruce A. Koplan, MD, MPH,* Andrew J. Kaplan, MD,† Stan Weiner, MD,‡ Paul W. Jones, Milan Seth, MS,∥ Shelly A. Christman, PhD§

Boston, Massachusetts; Mesa, Arizona; Tyler, Texas; and St. Paul and Brooklyn Park, Minnesota

Figure 2: Survival Free From Heart Failure Hospitalization and All-Cause Mortality in All Patients
Figure 2: When assessed by quartiles, patients with biventricular pacing percentage above 99.8% experienced a 24% reduction in mortality compared to the other quartile groups (HR=0.76, p < .001). Patients with less than 99.8% biventricular pacing had a 19% increase in mortality (HR=1.19, p < .001).

- **Perfect (complete) BIV delivery**
  - Carvedilol 50 x 2
  - Enalapril 20 mg x 2

- **Ineffective BIV delivery**
  - Carvedilol 3.25 mg
  - Enalapril 2.5 mg

- **“Good (acceptable)”delivery**
  - Carvedilol 12.5 mg x 2
  - Enalapril 7.5 mg x 2
To ↓ the incidence of non responders to CRT

PRE-CRT
(Correct Selection)

POST-CRT
(Follow up)

Home remote monitoring

BIV pacing %
Arrhythmias
Optivol
Shocks

HF

EP

Patient
CONCLUSIONS

→ At present time there is no univocal definition of non responders to CRT

→ It’s undeniable and obvious that patients may remain unchanged or even worsened after CRT ....

→ Real non responders are patients who remain unchanged or even ameliorated when CRT is switched OFF!

→ After CRT, every effort should be made by EP and HF specialists to optimize both device programming and medical therapy to maximize CRT response
Correct strategy to ↓ non-responders to CRT

Maximal tolerated drug therapy

(Maximal electrical therapy

(100% BIV pacing)

At implantation, immediately after implantation and at every outpatient clinic f.u., TRY TO MAXIMIZE BOTH PHARMACOLOGIC & ELECTRICAL THERAPY