Is QRS width predictive of the clinical and echocardiographic response to chronic CRT in mildly symptomatic HF patients?

Data from REVERSE

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Introduction

- Cardiac resynchronisation therapy (CRT) : guidelines-established therapy in moderate to severe heart failure (HF) patients with depressed left ventricular (LV) systolic function and evidence of ventricular dyssynchrony

- To date, QRS duration (QRSd) is the only recommended dyssynchrony marker to select patients for CRT :
  \[
  \text{QRS} \geq 120\text{ms}
  \]

- 30% of HF patients have a QRS $\geq 120\text{ms}$ \(^{(1)}\)

- Prolonged QRS associated with:
  - Depressed LV systolic function \(^{(2)}\)
  - Increased all cause mortality rate \(^{(3)}\)

- QRS progression associated with:
  - Worsening NYHA functional class \(^{(4)}\)
  - Earlier mortality if QRS increases $>5\text{ms/year}$ \(^{(5)}\)

1. Juliano et al. AHJ 2002;143:1085-91
2. Shenkman et al. Chest 2002;122;528-34
4. Baldasseroni et al. AHJ 2002;143:398-405
5. Xiao et al. IJC 1996;53:163-70
1. Is QRSd at baseline predictive of the response to CRT?
   - Yes in observational studies (1,2)
   - No clear evidence in RCT’s in class III-IV patients (3,4,5)

2. Is « acute » (immediately after CRT implant) QRS change predictive of the response to CRT?

3. Is « chronic » (during follow-up) QRS change predictive of the response to CRT?

Randomized Controlled Trials in NYHA III-IV patients:
- wide mean QRSd
- small interindivdual differences
- low proportion of patients with QRS<150ms
Controversial issues

1. Is QRSd at baseline predictive of the response to CRT?

2. Is « acute » post-implant QRS change predictive of the response to CRT?
   - Yes (1,2)
   - No (3)

3. Is « chronic » (during follow-up) QRS change predictive of the response to CRT?

   « Immediately after implantation of the pacemaker, there was a trend towards a larger reduction in QRS duration in the responders, although not significant (p=0.07) »

   (3)

Positive correlation

Lack of significant evidence

2. Alonso et al. AJC 1999;84:1417-21
Controversial issues

1. Is QRSd at baseline predictive of the response to CRT?

2. Is «acute» (immediately after CRT implant) QRS change predictive of the response to CRT?

3. Is «chronic» post-implant QRS change predictive of the response to CRT?
   - Yes (1)
   - No (2)

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1. Lecoq et al. EHJ 2005;26:1094-1100
2. Reuter et al. AJC 2002;89:346-50
• Accuracy and reproducibility of QRSd measurement on surface ECG

• Predictive value on the clinical and echo response to CRT of:
  ➢ Baseline QRSd
  ➢ Acute change after CRT: discharge (D) - baseline (B)
  ➢ Chronic change after CRT: 12-months (12m) - baseline (B)
REVERSE study

- REVERSE study \(^{(1)}\): 610 patients, NYHA II or I-stage C (previously symptomatic), LV ejection fraction (LVEF) ≤ 40%, QRS ≥ 120ms, on optimal medical therapy
  - Randomization 2:1 to CRT ON or CRT OFF after CRT device implantation in all subjects
  - Primary endpoint: clinical composite response (CCS) at 1 year \(^{(2)}\)

Clinical Composite Response:
- death
- hospitalisation for HF
- cross over or permanently discontinued double-blind treatment because of worsening HF
- NYHA class change
- patient global assessment at 1 year

1. Linde et al. JACC 2008;52:1834-43
2. Packer et al. JCardFail 2001;7:176-82
REVERSE study

• REVERSE study (1): 610 patients, NYHA II or I-stage C (previously symptomatic), LV ejection fraction (LVEF) ≤ 40%, QRS ≥ 120ms, on optimal medical therapy
  • Randomization 2:1 to CRT ON or CRT OFF after CRT device implantation in all subjects
  • Primary endpoint: clinical composite response (CCS) at 1 year (2)
  • Clinical responder: « improved » or « unchanged »
  • Pre-specified secondary endpoint: LV endsystolic volume index change (LVESVi) at 1 year
  • Echocardiographic (echo) responder = LVESVi decrease ≥ 15% and/or LVEF increase ≥10%

1. Linde et al. JACC 2008;52:1834-43
2. Packer et al. JCardFail 2001;7:176-82
Methods: ECG analysis

- Among the REVERSE study population, 511 patients (83.8% of the total population) with complete data set and good quality ECG recordings.
- Core center analysis of baseline (B), discharge (D) and 12-months (12m) ECG’s by experienced operator unaware of patient’s randomisation order and outcome.
- Analysis on a tracer table, mean QRSd calculated from 9 cardiac cycles in leads II, V1 and V6 (maximum of 3 cycles in each lead).

**REVERSE baseline:**
Mean QRSd: 151.7 ± 22.6 ms
% QRSd <150ms: 44.2%
ECG analysis: reproducibility

Reproducibility of the measure
- 50 random ECG with intrinsic and paced QRS, at two paper speeds (25 and 50mm/s)
- Analysed twice by the same operator (intra-observer), and compared with a second analysis by an other operator (inter-observer)

<table>
<thead>
<tr>
<th></th>
<th>Intrinsic conduction/paced QRS</th>
<th>ECG paper speed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-paced QRS</td>
<td>BiV paced</td>
</tr>
<tr>
<td><strong>Coefficient of variation (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intra-observer variability</strong></td>
<td>1,6 %</td>
<td>6,4 %</td>
</tr>
<tr>
<td><strong>Inter-observer variability</strong></td>
<td>1,4 %</td>
<td>2,6 %</td>
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</tbody>
</table>
QRSd at baseline and clinical / echo response to CRT

<table>
<thead>
<tr>
<th>QRSd at baseline (ms)</th>
<th>Clinical response</th>
<th>Echocardiographic response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Responder</td>
<td>Non responder</td>
</tr>
<tr>
<td>153,2 ± 21,7</td>
<td>158,7 ± 20,3</td>
<td>&lt;0,0001</td>
</tr>
<tr>
<td>141,2 ± 23,3</td>
<td>143,7 ± 22,4</td>
<td>&lt;0,0001</td>
</tr>
</tbody>
</table>
Baseline QRSd and clinical / echo response to CRT

### CRT ON group

<table>
<thead>
<tr>
<th>QRSd at baseline (ms)</th>
<th>Total number of patients</th>
<th>Improved/Unchanged</th>
<th>Worsened</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 150</td>
<td>137</td>
<td>108 (78,9%)</td>
<td>29 (21,1%)</td>
</tr>
<tr>
<td>150 - 180</td>
<td>144</td>
<td>132 (91,7%)</td>
<td>12 (8,3%)</td>
</tr>
<tr>
<td>&gt; 180</td>
<td>31</td>
<td>29 (93,5%)</td>
<td>2 (6,5%)</td>
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</table>

p-value for Cochran-Mantel-Hanszel test = 0,002

### Echo responder

<table>
<thead>
<tr>
<th>QRSd at baseline (ms)</th>
<th>Total number of patients</th>
<th>Echo responder</th>
<th>Echo non responder</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 150</td>
<td>120</td>
<td>42 (35,0%)</td>
<td>78 (65,0%)</td>
</tr>
<tr>
<td>150 - 180</td>
<td>126</td>
<td>86 (68,3%)</td>
<td>40 (31,7%)</td>
</tr>
<tr>
<td>&gt; 180</td>
<td>29</td>
<td>20 (69,0%)</td>
<td>9 (31,0%)</td>
</tr>
</tbody>
</table>

p-value for Cochran-Mantel-Hanszel test < 0,0001

**Echo responder = LVESVi decrease ≥ 15% and/or LVEF increase ≥10% at 12 months**
Acute QRS change after CRT implantation and clinical / echo response to CRT

### Acute QRS change: QRSd Discharge (D) - Baseline (B)

<table>
<thead>
<tr>
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<th>Clinical response</th>
<th>Echocardiographic response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Responder</td>
<td>Non responder</td>
</tr>
<tr>
<td>Acute QRS change D-B</td>
<td>-7.7 ± 26.1</td>
<td>-2.3 ± 24.6</td>
</tr>
</tbody>
</table>
Acute QRS change after CRT implantation and death or HF hospitalization

- Bigger acute QRS change is associated with decrease in HF hospit \((p=0.02)\) and death + HF hospit \((p=0.028)\)

- 3 equal-sized groups for death / HF hospit incidence of acute QRS change:
  - High: decrease 21.8 - 63.2 ms
  - Mid: decrease 21.5 - increase 0.3 ms
  - Low: increase 0.3 - 65.8 ms

Acute QRS change: QRSd Discharge (D) - Baseline (B)
Chronic QRS change during CRT and clinical /echo response to CRT

Chronic QRS change: QRSd 12-months (12m) - Baseline (B)

<table>
<thead>
<tr>
<th>QRS change (ms) 12m - B</th>
<th>Clinical response</th>
<th>Echocardiographic response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Responder</td>
<td>Non Responder</td>
</tr>
<tr>
<td>-4.5 ± 26.2</td>
<td>5.3 ± 27.9</td>
<td>0.025</td>
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Conclusion

- Acceptable reproducibility of QRS width measurement using a tracer table
- REVERSE (like MADIT-CRT) shows that QRSd at baseline is predictive of the clinical and echo response to CRT in mildly symptomatic HF patients
- Acute and chronic QRS narrowing after CRT are associated with greater likelihood to respond
Controversial issues

QRS width measurement on surface ECG

- Where and how to measure QRSd: still not internationally standardized (1)
- Methodology in multicenter studies: variable or not reported (2)
- Low accuracy of manual (visual or ECG-ruler) vs automatic methods (3)
- Accuracy may be improved using caliper or digitized ECGs (4)
- Even computerized methods show differences (5)
- Intra- and inter-observer reproducibility?

1. Kligfield et al. JACC 2007;49:1109-27