Prediction of Cardiac Resynchronization Therapy Response with Cardiac $^{123}$I-mIBG imaging in Patients with Heart Failure

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Disclosure

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- Dr. Martin J. Schalij receives grants from Biotronik, Boston Scientific & Medtronic

- The remaining authors: none
Cardiac resynchronization therapy (CRT) is the recommended therapy for patients with advanced heart failure (HF) in NYHA functional class III-IV despite optimal medical therapy, LVEF $\leq 35\%$ and QRS duration $>120\text{ms}^1$

30-40% of CRT patients do not show significant response despite fulfilling current guidelines$^2$

Recent focus has been on the search for better selection criteria and understanding of mechanisms underlying CRT response

$^1$Epstein AE et al, J Am Coll Cardiol 2008

Background

- Abnormalities in cardiac sympathetic nervous system are observed in HF patients

- In myocardium of patients with LV dysfunction,
  - ↑ sympathetic drive with ↑ amount of norepinephrine (NE) in the synaptic cleft
  - ↓ pre-synaptic NE reuptake and expression of NE transporter as a result of post-transcription downregulation
  - Downregulation of post-synaptic β-adrenoceptor density

- 123-iodine meta-iodobenzylguanidine (¹²³I-mIBG), an analogue of NE, is a commonly used non-invasive imaging agent for evaluation of cardiac sympathetic innervation and denervation
Background

- $^{123}$I-mIBG, shares the same uptake, release and storage mechanism as NE but it itself does not undergo metabolism.

- Myocardial uptake and distribution can thus be imaged.

- Numerous studies\(^1\)-\(^3\) have demonstrated that reduced myocardial $^{123}$I-mIBG uptake is an independent predictor of adverse outcome in HF patients.

- Studies have also shown that improvement of cardiac $^{123}$I-mIBG uptake can be observed after anti-HF therapy, including CRT\(^4\).

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3. Jacobson AF et al, JACC 2010
4. Erol-Yilmaz et al, PACE 2005
Background

- It is not clear whether baseline cardiac sympathetic abnormality as assessed using myocardial $^{123}$I-mIBG play a role in LV reverse remodelling post CRT

- **Aim of the study:**

  To evaluate the prognostic usefulness of baseline myocardial $^{123}$I-mIBG parameters in prediction of CRT response at 6 months
Patient selection

- Consecutive, advanced symptomatic HF patients who were referred for CRT
- Exclusion criteria: existing PPM or ICD
- Patients were
  - Stable on maximal doses of medications ≥2 months prior to CRT implantation
  - Ischemic etiology = presence of significant coronary artery disease (≥50% stenosis) or a history of myocardial infarction or revascularization
- Clinical and transthoracic echocardiographic assessment were performed both at baseline and at 6 months
- All patients underwent myocardial $^{123}$I-mIBG imaging at baseline
Baseline parameters

Echocardiography

- LV end-diastolic volume
- LV end-systolic volume
- LV ejection fraction (Simpson’s rule\(^1\))
- LV dyssynchrony (maximal basal septal-lateral wall delay\(^2\))

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1Lang RM et al, J Am Soc Echocardiogr 2005
2Bax JJ et al, Am J Cardiol 2003
Baseline parameters

Cardiac $^{123}$I-mIBG

- Early (15 mins):
  - Planar heart-to-mediastinum (H/M) ratio
  - $^{123}$I-mIBG SPECT score\(^1\)
    (based on 17-segment and score of 0-4 for each segment)

- Late (4 hour):
  - Planar H/M ratio
  - Myocardial washout ratio\(^1\) = 
    $\frac{(\text{early H/M ratio} - \text{(late H/M ratio)})}{\text{(early H/M ratio)}} \times 100$
  - $^{123}$I-mIBG SPECT score\(^1\)

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\(^1\)Bax JJ et al, Circ Cardiovasc Imaging 2008

Primary endpoint

- Response to CRT:
  - Significant LV reverse remodelling with a reduction of ≥15% in LVESV at 6 months post-CRT implantation
Study population

101 patients referred for CRT

- 4 patients died before echo
- 3 patients lost to follow-up at 6 months

Final population: 94 patients
6 months post-CRT

- 60% (56/94) of patients showed a reduction of ≥15% in LVESV
Baseline clinical characteristics
Responders versus Non-responders

<table>
<thead>
<tr>
<th></th>
<th>All (n=94)</th>
<th>Responders (n=56)</th>
<th>Non-responders (n=38)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>67 (71.3%)</td>
<td>39 (69.6%)</td>
<td>28 (73.7%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Age, years</td>
<td>66.7 ± 8.7</td>
<td>65.9 ± 8.5</td>
<td>67.8 ± 8.9</td>
<td>0.30</td>
</tr>
<tr>
<td>Body mass index, kgm⁻²</td>
<td>27.2 ± 4.0</td>
<td>27.2 ± 3.9</td>
<td>27.2 ± 4.3</td>
<td>0.93</td>
</tr>
<tr>
<td>Ischemic etiology, n (%)</td>
<td>67 (71.3%)</td>
<td>34 (60.7%)</td>
<td>33 (86.8%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>34 (36.2%)</td>
<td>23 (41.1%)</td>
<td>11 (28.9%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Hypercholesterolaemia, n (%)</td>
<td>27 (28.7%)</td>
<td>18 (32.1%)</td>
<td>9 (23.7%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>16 (17.0%)</td>
<td>8 (14.3%)</td>
<td>8 (21.1%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>25 (26.6%)</td>
<td>14 (25.0%)</td>
<td>11 (28.9%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
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<tr>
<td>Diuretics, n (%)</td>
<td>87 (92.6%)</td>
<td>50 (89.3%)</td>
<td>37 (97.4%)</td>
<td>0.23</td>
</tr>
<tr>
<td>ACEi / ARB, n (%)</td>
<td>81 (86.2%)</td>
<td>46 (82.1%)</td>
<td>35 (92.1%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Beta-blockers, n (%)</td>
<td>68 (72.3%)</td>
<td>42 (75.0%)</td>
<td>26 (68.4%)</td>
<td>0.48</td>
</tr>
<tr>
<td>NYHA functional class III, n (%)</td>
<td>92 (97.5%)</td>
<td>55 (98.2%)</td>
<td>37 (97.4%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Quality-of-life score</td>
<td>31.7 ± 16.8</td>
<td>32.8 ± 17.6</td>
<td>30.0 ± 15.6</td>
<td>0.45</td>
</tr>
<tr>
<td>6-minute walk test, m</td>
<td>342.4 ± 103.9</td>
<td>343.1 ± 100.1</td>
<td>341.4 ± 110.9</td>
<td>0.94</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>157.1 ± 34.2</td>
<td>156.8 ± 32.6</td>
<td>157.5 ± 37.0</td>
<td>0.93</td>
</tr>
</tbody>
</table>
Baseline $^{123}$I-mIBG imaging characteristics

Responders versus Non-responders

<table>
<thead>
<tr>
<th></th>
<th>All (n=94)</th>
<th>Responders (n=56)</th>
<th>Non-responders (n=38)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
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</tr>
<tr>
<td>LVEDV, mL</td>
<td>218.9 ± 77.0</td>
<td>229.2 ± 77.9</td>
<td>203.8 ± 74.1</td>
<td>0.12</td>
</tr>
<tr>
<td>LVESV, mL</td>
<td>163.9 ± 66.0</td>
<td>170.7 ± 67.1</td>
<td>154.0 ± 64.0</td>
<td>0.23</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>27.5 ± 7.9</td>
<td>27.1 ± 7.1</td>
<td>28.1 ± 8.9</td>
<td>0.54</td>
</tr>
<tr>
<td>LV dyssynchrony, ms</td>
<td>65.9 ± 43.0</td>
<td>73.8 ± 42.7</td>
<td>54.3 ± 41.3</td>
<td><strong>0.030</strong></td>
</tr>
<tr>
<td><strong>$^{123}$I-mIBG imaging</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Early H/M ratio</td>
<td>1.54 ± 0.20</td>
<td>1.59 ± 0.21</td>
<td>1.48 ± 0.18</td>
<td><strong>0.009</strong></td>
</tr>
<tr>
<td>Late H/M ratio</td>
<td>1.42 ± 0.20</td>
<td>1.48 ± 0.20</td>
<td>1.33 ± 0.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial Washout rate, %</td>
<td>8.0 ± 6.2</td>
<td>6.6 ± 5.5</td>
<td>10.0 ± 6.6</td>
<td><strong>0.008</strong></td>
</tr>
<tr>
<td>Early summed SPECT defect score</td>
<td>22.4 ± 9.6</td>
<td>20.4 ± 8.9</td>
<td>25.6 ± 9.9</td>
<td><strong>0.010</strong></td>
</tr>
<tr>
<td>Late summed SPECT defect score</td>
<td>28.2 ± 8.9</td>
<td>26.9 ± 8.4</td>
<td>30.4 ± 9.4</td>
<td><strong>0.070</strong></td>
</tr>
</tbody>
</table>
Interpretation

- 60% of patients showed a reduction of ≥15% in LVESV

- Responders were:
  - Less likely to have ischemic etiology
  - More extensive LV dyssynchrony at baseline
  - Higher early and late H/M ratios at baseline
  - Lower myocardial washout rates at baseline
  - Lower early $^{123}$I-$m$IBG SPECT defect scores at baseline
## Univariate and multivariate baseline predictors of CRT response

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Ischemic etiology</td>
<td>0.234</td>
<td>0.079 – 0.691</td>
</tr>
<tr>
<td>LV dyssynchrony</td>
<td>1.011</td>
<td>1.001 – 1.022</td>
</tr>
<tr>
<td>Early H/M ratio (per 0.1 unit increase)</td>
<td>1.349</td>
<td>1.070 – 1.700</td>
</tr>
<tr>
<td>Late H/M ratio (per 0.1 unit increase)</td>
<td>1.591</td>
<td>1.224 – 2.067</td>
</tr>
<tr>
<td>Myocardial washout rate</td>
<td>0.907</td>
<td>0.841 – 0.978</td>
</tr>
<tr>
<td>Early summed $^{123}$I-mIBG SPECT defect score</td>
<td>0.941</td>
<td>0.897 – 0.988</td>
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</tbody>
</table>
Example (1)

66 year-old male with dilated cardiomyopathy

Late H/M ratio 1.77

Mediastinum ROI

Heart ROI

Pre CRT

Post CRT
Example (2)

75 year-old male with history of myocardial infarct

Late H/M ratio 1.12
Conclusions

- In patients with advanced HF, baseline high late myocardial uptake (planar H/M ratio) is associated with greater likelihood of favourable response to CRT.

- This study suggests that denervated myocardium are less likely to reverse remodel following CRT.

- \(^{123}\)I-mIBG may serve as an additional selection tool to predict CRT response.
More severe cardiac sympathetic abnormalities, less CRT response... Why?

Cardiac $^{123}$I-mIBG uptake reflects the extent and severity of myocardial denervation (which serves as a marker of significant myocardial injury) as its uptake requires presence of intact neuronal integrity (i.e. NE reuptake-1 transporters)

1. Loss of $^{123}$I-mIBG uptake in denervated myocardium and ↓$^{123}$I-mIBG uptake in ischemic myocardium

2. Alteration in NE kinetics occurs in chronic HF (irrespective of underlying etiology) when myocardium is ‘under stressed’ or injured

3. Function of presynaptic NE reuptake-1 transporters may be impaired in failing hearts (for example – depleted intracellular adenosine triphosphate)