Presentation title: The Development of CRT

Speaker: John GF Cleland

Conflicts of interest: I have received research support and honoraria from Biotronik, Boston Scientific, Medtronic, Sorin (LivaNova), St Jude (Abbott)

Presentation slide distribution: (please delete as applicable)

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The Development of CRT

John GF Cleland
Glasgow & London
• Ventricular dyssynchrony due to conduction disorders
  • Wolferth & Margolies AHJ 1935

• Pacing-induced Dyssynchrony
  • Haber & Leatham. BHJ 1965
  • Gibson et al BHJ 1971

• Treatments for Dyssynchrony
  • Surgical
    • Gibson, Greenbaum, Pridie & Yacoub. BHJ 1988
  • Pharmacological
    • Andersson, Caidahl, Waagstein. Cardiology 1994
pacing site caused little or no change in systemic arterial pressure or cardiac output. However, the rate of movement of the ball of the prosthesis at the onset of left ventricular ejection was consistently greater during biventricular pacing than during pacing of the right ventricle alone, with intermediate values during left ventricular pacing. This provides evidence for the development of an increased force by the left ventricle at the onset of systole during biventricular pacing, resulting from a more synchronous contraction, and shows that such changes may occur in the absence of any alteration in the external work done by the left ventricle.
N = 12
Observational

Effects of dual-chamber pacing with short atrioventricular delay in dilated cardiomyopathy

Stephen J. D. Brecker  Han B. Xiao  Jane Sparrow  Derek G. Gibson

The improvements in ventricular filling characteristics were associated with striking changes in exercise duration (from 304 [SD 112] s at the longer atrioventricular interval increased by a mean of 104 [45–165] s, p < 0.05), maximum
First cases of atrio-bioventricular pacing (aka cardiac resynchronization therapy)

- Auricchio (PACE 1993)
- Bakker (PACE 1994)
- Cazeau (Pacing Clin Electrophysiol 1994)
Mustic

MUltisite STimulation In Cardiomyopathy

Prof. Jean-Claude DAUBERT, Rennes, France

ESC XXII\textsuperscript{nd} Congress - Amsterdam - August 29\textsuperscript{th} 2000

(N Engl J Med 2001;344:873-80.)
Mustic Cross-Over

6-minute walk (m)

Single-Blind
48 patients in sinus rhythm
3 month treatment periods

Δ = + 23 %
p = 0.0001

Baseline
Random
CO1
CO2

B iV - N o P
N o P - B i V

320
354
346
316
336
384
413
# Patient Preference

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>BiV pacing</td>
<td>n = 41</td>
<td>n = 34</td>
</tr>
<tr>
<td></td>
<td>(86%)</td>
<td>(83%)</td>
</tr>
<tr>
<td>Inactive BiV</td>
<td>n = 2</td>
<td>n = 5</td>
</tr>
<tr>
<td></td>
<td>(4%)</td>
<td>(12%)</td>
</tr>
<tr>
<td>No Preference</td>
<td>n = 5</td>
<td>n = 2</td>
</tr>
<tr>
<td></td>
<td>(10%)</td>
<td>(5%)</td>
</tr>
</tbody>
</table>

**Sinus Rhythm**

- n = 48

**Atrial Fibrillation**

- n = 41

$p = 0.001$
### Substantial Randomized Controlled Trials of CRT-P/CRT-D compared to no Device

<table>
<thead>
<tr>
<th>Comparison</th>
<th>NYHA</th>
<th>SR</th>
<th>QRS (msec)</th>
<th>LVEF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COMPANION</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CRT-P (n = 617)</td>
<td>III/IV</td>
<td>Yes</td>
<td>Entry &gt;120 Median 160</td>
<td>Entry &lt;35 Median 20</td>
</tr>
<tr>
<td>CRT-D (n = 595)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Device (n = 308)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CARE-HF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT-P (n = 409)</td>
<td>III/IV</td>
<td>Yes</td>
<td>Entry &gt;120 Median 160</td>
<td>Entry &lt;35 Median 25</td>
</tr>
<tr>
<td>No Device (n = 404)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

- Reduced Mortality by ~40%
- Improved Symptoms & QoL
- Improved Exercise Capacity
- Increased Systolic BP (median ~7mmHg = many double-digit rise)
- Improved LV Function
- Reduced (Functional Systolic) Mitral Regurgitation !!!
## Substantial Randomized Controlled Trials of ICD versus CRT-D

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Blind</th>
<th>SR</th>
<th>NYHA</th>
<th>QRS (msec)</th>
<th>LVEF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>REVERSE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT # (n = 419)</td>
<td>Yes@</td>
<td>Yes</td>
<td>I (18%)</td>
<td>Entry &gt;120&lt;br&gt;Median 154</td>
<td>Entry &lt;40&lt;br&gt;Median 26</td>
</tr>
<tr>
<td>Con. # (n = 191)</td>
<td></td>
<td></td>
<td>II (82%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MADIT-CRT</td>
<td>No</td>
<td>Yes</td>
<td>I (15%)</td>
<td>Entry &gt;130&lt;br&gt;Median ~160</td>
<td>Entry &lt;30&lt;br&gt;Median 24</td>
</tr>
<tr>
<td>CRT-D (n = 1,089)</td>
<td></td>
<td></td>
<td>II (85%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD (n = 731)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAFT</td>
<td>No</td>
<td></td>
<td>II (80%)</td>
<td>Entry &gt;120&lt;br&gt;Median 158</td>
<td>Entry &lt;30&lt;br&gt;Median 23</td>
</tr>
<tr>
<td>CRT-D (n = 894)</td>
<td></td>
<td></td>
<td>III (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD (n = 904)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echo-CRT</td>
<td>Yes@</td>
<td>Yes</td>
<td>III 92%</td>
<td>Entry &lt;130&lt;br&gt;Median 106</td>
<td>Entry &lt;35&lt;br&gt;Median 27</td>
</tr>
<tr>
<td>CRT-D (n = 404)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD (n = 405)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

In REVERSE >80% of devices were CRT-D and <20% were CRT-P.

@ CRT was programmed on or off in a double-blind fashion.
How Does CRT Work?

- Which of these mechanisms is most important?
  - Prevent bradycardia
  - Shorten the AV interval
    - Pump primes LV & RV
    - Reduces diastolic MR
  - Pace the RV and the LV
    - Prevent AV block
  - Alter the timing of RV and LV free wall contraction and relaxation
    - Improve ventricular efficiency
    - Reduce functional systolic MR (with luck) if present
    - Reduce diastolic MR
  - Raises systolic blood pressure (& improves haemodynamics)
    - By one or more of the above mechanisms

- Does the importance of each mechanism vary from one patient to the next?

- Does the importance of each mechanism vary depending on context or time?
Figure 8 Clinical factors influencing the likelihood to respond to CRT.
Individual Patient Data Meta-Analyses of RCTs for CRT

Greater benefit if:
- Older
- Female
- Longer QRS Duration

- 3,782 patients:
- QRS duration was the ONLY predictor of CRT benefit

Who Should Have CRT?

• Informed patients who agree with your therapeutic goals!

• Therapeutic Goals
  • Improvement in symptoms / well-being?
  • Delaying or preventing decline?
  • Increased longevity?
  • Improving left ventricular ejection fraction?

• Concomitant Procedures
  • Implantable Defibrillator
  • Cardiac Surgery

• Therapeutic Substrate
  • Dilated LV with a Reduced LVEF
  • Sinus Rhythm
  • QRS Duration at least 130msec
  • (Congestion Requiring Diuretic Therapy)
  • (Mitral Regurgitation)

• Guidelines

Change in LV Function
  • is a poor measure of outcome in trials of CRT
  Depends more on
  • aetiology of LV dysfunction than on effect of CRT
Managing Disappointment

• Managing expectations
  • Patients
  • Colleagues
  • Your Own

• Learning from experience
  • Don’t be deceived by superficial appearances
  • Disappointing outcome ≠ lack of response

• Care at Implantation
  • LV lead position
  • Rise in Systolic BP
  • Quadripolar leads

• Programming?

• Pharmacological Treatment
What Next?

- LV Lead Position
  - Anatomical Position
  - Physical Separation
  - Physiological
  - Scar
- Quadripolar Pacing
- Multisite Pacing
- ADAPTIVE-CRT
- Leadless Pacing
- His-Bundle Pacing
Study Design

HOPE-HF is a
- Multicentre
- Prospective
- Randomised
- Double blinded
- Cross over study

The study will recruit a sub-population of patients with Heart Failure from around 20 investigational sites in the UK

Whinett Z et al. JACC: Clinical Electrophysiology, Volume 1, Issue 6, 2015, 582–591
UK CRT implants by age - 2012

*CRT-D not Superior to CRT-D*
- **COMPANION**
- **DANISH**
BCS CSG

- REVIVED
- HOPE-HF
- IRONMAN
- CMR-Guide
- BeAT-HF
- RESHAPE-2
- RELIEHF
- Q10-HF?

Representatives
- Each CRN
- Each Nation
- PAM
- PPI
- CRN
- CTU / R&D

Heart Research Days
- Wednesday prior to BSH
- Wednesday after BCS
All-Cause Mortality

**ICD v Control (No CRT)**

Hazard Ratio = 0.83 (0.58 - 1.19)
p-value = 0.31

**CRT-D v CRT-P**

Hazard Ratio = 0.91 (0.64 - 1.29)
p-value = 0.59

**SCD-HeFT: Mortality by Intention-to-Treat**

Hazard Ratio = 0.96 (0.80 - 1.13)
p-value = 0.529

<table>
<thead>
<tr>
<th>Months of Follow up</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>0.13</td>
<td>0.21</td>
<td>0.28</td>
<td>0.35</td>
<td>0.42</td>
<td>0.49</td>
<td>0.56</td>
</tr>
<tr>
<td>ICD Therapy</td>
<td>0.12</td>
<td>0.20</td>
<td>0.27</td>
<td>0.34</td>
<td>0.42</td>
<td>0.49</td>
<td>0.56</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.14</td>
<td>0.22</td>
<td>0.29</td>
<td>0.36</td>
<td>0.43</td>
<td>0.50</td>
<td>0.57</td>
</tr>
</tbody>
</table>

**ICD**

<table>
<thead>
<tr>
<th>323</th>
</tr>
</thead>
</table>

**Controls**

<table>
<thead>
<tr>
<th>322</th>
</tr>
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</table>