Utilising CRT Algorithms - Can they improve CRT Response?

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Cardiac Resynchronisation Therapy (CRT)

- Reduces heart failure (HF) mortality by 40% on top of optimal medical therapy
- Decreases HF-related hospitalisations by 52%
CRT Response Rate

One-third of patients do not experience the full benefit of CRT\textsuperscript{1-6}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{chart.png}
\caption{Percentage of improved Clinical Composite Score for different CRT trials.}
\end{figure}

\begin{itemize}
\item MIRACLE\textsuperscript{1} 67%
\item MIRACLE ICD\textsuperscript{2} 52%
\item MIRACLE II ICD\textsuperscript{3} 58%
\item InSync III Marquis\textsuperscript{4}\textsuperscript{TM} 67%
\item PROSPECT\textsuperscript{5} 69%
\item FREEDOM\textsuperscript{6} 67%
\end{itemize}

\begin{itemize}
\item \textsuperscript{2} Young JB, et al. \textit{JAMA.} 2003;289:2685-2694.
\item \textsuperscript{5} Abraham WT, et al. \textit{Heart Rhythm.} 2005;2:S65.
\item \textsuperscript{6} Abraham WT, et al. Late-Breaking Clinical Trials, HRS 2010. Denver, Colorado.
\end{itemize}

\textsuperscript{*}AV optimized only
There are many drivers for CRT non-responders

Potential Reasons for Suboptimal CRT Response

- Percentage of Nonresponder Patients with These Findings

- Suboptimal AV Timing: 65%
- Arrhythmia: 60%
- Anemia: 55%
- Suboptimal LV Lead Position: 50%
- < 90% Biventricular Pacing: 45%
- Suboptimal Medical Therapy: 40%
- Persistent Mechanical Dyssynchrony: 35%
- Underlying Narrow QRS: 30%
- Compliance Issues: 25%
- Primary RV Dysfunction: 20%

Strategies to Improve CRT response

- Improve Patient Selection
- Device based optimisation
Multiple single centre studies have reported that echocardiographic parameters may better predict response. However, a randomised multicentre trial (Prospect) failed to show any viable echocardiographic parameter to predict response.

Why?
Strategies to Improve CRT response

- Improve Patient Selection
- Device based optimisation
Device based optimisation

• More recently focus has been shifting to device based optimisation

• Potential benefits over echo:
  • Simpler to perform
  • No inter-observer variability
  • Can optimise more frequently
Device Companies

- Boston Scientific: Expert Ease for Heart Failure
  Smart Delay

- St Jude: Quick Opt, MPP

- Medtronic: Adaptive CRT, EffectivCRT, Multiple Point Pacing

- Sorin: SonR, Multiple Point Pacing
Boston Scientific-Smart Delay

- Smart Delay provides both paced and sensed recommendations by accounting for three inputs:
  - Intrinsic AV intervals (Sensed AV and Paced AV intervals),
  - Interventricular timing (surface QRS duration)
  - LV lead location
- Algorithm was developed from the results of several previous acute clinical studies (PATH CHF, PATH CHF II, and SAVER)
Boston Sci-Smart AV Trial

Primary Endpoint - LVESV

Change in Volume (ml)

Smart Delay (n = 283)  Echo (n = 282)  Fixed (n = 281)

Background—One variable that may influence cardiac resynchronization therapy response is the programmed atrioventricular (AV) delay. The SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy (SMART-AV) Trial prospectively randomized patients to a fixed empirical AV delay (120 milliseconds), echocardiographically optimized AV delay, or AV delay optimized with SmartDelay, an electromagnetically based algorithm.

Methods and Results—A total of 914 patients (68% male; mean age, 65.1 ± 11 years; mean left ventricular ejection fraction, 25 ± 7%) who met enrollment criteria received a cardiac resynchronization therapy device, and 480 patients were randomized in a 1:1:1 ratio. All patients were programmed (GERD-40 or DDDR-40) and evaluated after implantation and 3 and 6 months later. The primary end point was left ventricular end-systolic volume. Secondary end points included New York Heart Association class, quality of life score, 6-minute walk distance, left ventricular end-diastolic volume, and left ventricular ejection fraction. The median (quartiles 1 and 3) for change in left ventricular end-systolic volume at 6 months for the SmartDelay, echocardiography, and fixed arms were 25 ml (15 and 45 ml), 19 ml (14 and 64 ml), and -15 ml (-11 and 41 ml), respectively. No difference in improvement in left ventricular end-systolic volume at 6 months was observed between the SmartDelay and echocardiography arms (P = 0.22) or the SmartDelay and fixed arms (P = 0.06). Secondary end points, including structural (left ventricular end-diastolic volume and left ventricular ejection fraction) and functional (6-minute walk, quality of life, and New York Heart Association classification) measures, were not significantly different between arms.

Conclusion—Neither SmartDelay nor echocardiography were 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.

Clinical Trial Registration (URL) http://www.clinicaltrials.gov. Unique identifier: NCT00670144.

Key Words: clinical trials, randomized ■ echocardiography ■ electrophysiology ■ heart failure ■ implantable cardioverter-depilibrators

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AV Optimization:

- QuickOpt optimisation measures the total P-wave duration of eight IEGM events for the A-Sense test
- Measured P-wave durations are averaged
- The QuickOpt algorithm uses a proprietary formula to calculate the optimal AV delays
VV Optimization:

1. QuickOpt optimisation measures eight IEGM events for each of the V Sense, RV Pace and LV Pace tests.
   • V Sense—measures intrinsic interventricular delay
   • RV Pace—measures conduction speed from right to left
   • LV Pace—measures conduction speed from left to right

2. Measurements from each test are averaged

3. The QuickOpt algorithm uses a proprietary formula to calculate the optimal VV delay
St Jude – Freedom Trial

- Randomised multicenter trial
- 1647 patients
- 1:1 randomisation to QuickOpt vs Standard care

<table>
<thead>
<tr>
<th>Intention-to-Treat</th>
<th>QuickOpt Optimization Treatment group</th>
<th>Control group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Failure Clinical Composite Score</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Improved</td>
<td>551</td>
<td>67.52%</td>
<td>559</td>
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<tr>
<td>Unchanged</td>
<td>76</td>
<td>9.31%</td>
<td>86</td>
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<tr>
<td>Worsened</td>
<td>189</td>
<td>23.16%</td>
<td>183</td>
</tr>
<tr>
<td>Total</td>
<td>816</td>
<td>100%</td>
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</table>
Medtronic AdaptivCRT

- Main goals are:
  - Achieve LV only pacing in patients with normal AV conduction
  - Achieve dynamic AV conduction to simulate normal AV function
  - To continually optimise AV and VV intervals to improve CRT response
  - P and QRS width measurements occur every 16 hr
  - AV Interval Measurements occur every minute
Normal AV

aCRT pre-paces LV & reduces RV pacing
aCRT senses shortening in AV & optimises CRT
aCRT automatically switches to Biv pacing
Adaptive CRT Trial

- 522 patients, prospective, multi-center, randomised double-blinded study
- aCRT vs Echo optimised CRT
Comparison to Echo optimisation

- Compared echo based optimisation (1 and 6 months) versus adaptive CRT.
Higher percentage Synchronized LV Pacing in the aCRT Arm had a lower rate of death and HF hospitalizations.
Improved clinical outcomes for patients with Normal AV Conduction

% Patient Improvement in Packer Clinical Composite Score

- 81% for AdaptivCRT with Normal AV intervals
- 69% for Control with Normal AV intervals

p = 0.041

% Improved Clinical Composite Score

- MIRACLE I: 67%
- MIRACLE ICD: 52%
- MIRACLE II ICD: 58%
- InSync III Marquis: 67%
- PROSPECT: 69%
- FREEDOM: 67%
AdaptivCRT Reduced AF Risk
As compared to patients receiving echo optimized CRT

\[ p = 0.03 \]
HR = 0.54 (0.31-0.93)

% Patients with ≥ 48 Hours of AT/AF

0% 10% 20% 30% 40% 50%
0 6 12 18 24 Months Since Randomization

Echo 16.2%
aCRT 8.8%

Number remaining

160 141 126 109 33
312 280 260 241 83

Sorin SonR

- Uses a hemodynamic sensor embedded in the atrial sense / pace lead, detects cardiac muscle vibrations that reflect the first heart sound

- The amplitude of the first heart sound reflects changes in contractility (LVdP/dtmax)
• Optimises VV & AV delays weekly

**Every Monday:**

• At 0:00am: search of the optimal VV configuration (7 VVd and 6 AVd)
• At 1:00am: search of the optimal sensed AV delay at rest (opt VVd and 11 AVd)
• At 2:00am: search of the optimal paced AV delay at rest (opt VVd and 11 AVd)
• At 12:00pm: search of the optimal AV delay at exercise (opt VVd and 5 Avd)
Sorin-CLEAR study

- Randomised Multicenter trial
- 238 patients 1:1 SonR vs standard practice

![Primary endpoint chart](chart.png)

- SonR group: 76% with improvement
- Control group: 62% with improvement
- p-value: 0.0285
RESPOND CRT study design

**DESIGN**
RESPOND-CRT is an International, Multicenter, Randomised (2:1), Prospective, Double-blinded trial

**PATIENTS**
- LVEF ≤ 35%
- QRS ≥ 120 ms in LBBB or QRS ≥ 150 ms in non-LBBB
- NYHA III or IV
- Without permanent AF

**ENROLLMENT**
- 125 sites in Europe, USA, Australia
- Jan 2012 – Oct 2014
- Long term follow up ongoing (2 years)
Response to CRT is based on a hierarchical set of clinical criteria
Primary efficacy end points at 12 months

- Improved: 75.0% (SonR) vs 70.4% (Echo AV & VV)
- Stable: 4.0% (SonR) vs 4.4% (Echo AV & VV)
- Worsened: 21.0% (SonR) vs 25.2% (Echo AV & VV)

Legend:
- SonR (n=649)
- Echo AV & VV (n=318)
<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>SonR (N=649)</th>
<th>Echo AV &amp; VV (N=318)</th>
<th>P value</th>
<th>Echo Better</th>
<th>SonR Better</th>
<th>Odds Ratio</th>
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<tr>
<td>Overall</td>
<td>75.0%</td>
<td>70.4%</td>
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<td>&lt;68.5 years</td>
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<td>76.1%</td>
<td>70.3%</td>
<td>0.27</td>
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<td>1.35</td>
</tr>
<tr>
<td>No</td>
<td>65.7%</td>
<td>72.0%</td>
<td></td>
<td></td>
<td></td>
<td>0.74</td>
</tr>
</tbody>
</table>
Difference in responder rate for subgroups

- Response Rate with Echo
- Additional benefit with SonR

- Age < 68.5
- Age ≥ 68.5
- Male
- Female
- BMI < 30
- BMI ≥ 30
- LVEF > 25%
- LVEF ≤ 25%
- LBBB
- Non LBBB
- QRS < 150 ms
- QRS ≥ 150 ms
- PR < 200
- PR > 200
- Ischemic
- Non Ischemic
- AF History
- No AF History
- Renal Dysfunction
- No Renal Dysfunction
- Diabetes
- No Diabetes
- Smoker
- Non Smoker
- Betablocker
- No Betablocker

+22% in patients with AF history
+16% in patients with renal dysfunction

Statistically significant
Multi Point Pacing

- Pacing from **two** LV sites ("Multipoint LV stimulation") and **one** RV
  - Capture a larger area
    - Engage areas around scar tissue
  - Improve pattern of depolarisation/repolarisation
  - Improve hemodynamics
  - Improve resynchronisation

- Using MPP does appear to reduce battery life by around 6-12 months
Acute data for MPP

- Hemodynamic benefit:
  A study of 44 patients by Pappone et al. showed MultiPoint Pacing significantly improved acute LV hemodynamic parameters assessed with pressure-volume loop measurements.

- Mechanical benefit:
  Biventricular pacing with MultiPoint LV pacing reduced mechanical dyssynchrony measured with tissue Doppler in a multicenter study of 41 patients.

- Electrical benefit:
  MultiPoint pacing was able to recruit a greater portion of the LV than traditional biventricular pacing, resulting in reduced activation times and QRS duration.
12-MONTH CRT RESPONSE RATE

Response definition:
ESV reduction ≥ 15% and Alive Status

Conventional Group (N = 21)
- 57% Responders
- 43% Non-responders

MultiPoint™ Pacing Group (N = 21)
- 76% Responders
- 24% Non-responders

19% Higher Absolute Response
44% Relative Reduction in Non-responder
MPP IDE Study

Safety and Efficacy of MultiPoint Pacing in Cardiac Resynchronization Therapy: The MultiPoint Pacing (MPP) IDE Trial

*Gery Tomassoni¹, James Baker II², Raffaele Corbisiero³, Charles Love⁴, David Martin⁵, Robert Sheppard⁶, Seth J. Worley⁷, Niraj Varma⁸, and Imran Niazi⁹ on behalf of the MPP IDE Investigators

¹Lexington Cardiology at Central Baptist, Lexington, KY, USA, ²Saint Thomas Research Institute, Nashville, TN, USA, ³Deborah Heart and Lung, Browns Mills, NJ, USA, ⁴NYU Langone Medical Center, New York, NY, USA, ⁵Lahey Clinic Medical Center - Cardiology, Burlington, MA, USA, ⁶The Heart Institute, St. Petersburg, FL, USA, ⁷Lancaster Heart Foundation, Lancaster, PA, USA, ⁸Cleveland Clinic Foundation, Cleveland, OH, USA, ⁹Aurora Cardiovascular Services, Milwaukee, WI, USA

*Advisor, Speaker, Medical Device Board: SJ Medical, Biosense Webster, Medtronic, Boston Scientific, Biotronics, Siemens, STXS, Topera, Atricure & Pfizer
Study Flow and Disposition
Prospective, Multicenter, Randomized, Double Blind Controlled Trial

Subject Enrolled
N=506

- Death N=2
  - Subjects withdrawn N=35
  - Unsuccessful Implant N=14

Quadripolar System Implant
(BiV programmed)
N=455

- Withdrawal prior to randomization N=11
- Death prior to randomization N=11

Randomization
(3 months)
- Subjects with acute Echo EA VTI, MPP ≥ BiV
- randomization was 1:1 stratified by the responder status
  N=381

- Observational Arm
  N=52
  - Not randomized due to results of acute echo EA VTI

MPP Arm
N=201*
followed for 6 months

1° Endpoint Evaluation
(9 months)

BiV Arm
N=180*
Followed for 6 months

1° Endpoint Evaluation
(9 months)

* Difference in N due to size of permuted blocks during randomization
Conclusions

- Echo based optimisation has very little evidence base for routine clinical work

- Device based algorithms are becoming more common and in initial trials do appear to confer some increased benefit

- Multi point LV pacing may also improve response but does have effect on battery life

- No head to head data across the different companies
Thank You..