CRT: NON-RESPONDERS OR NON-PROGRESSORS?

DON’T FORGET TO OPTIMISE DEVICE PROGRAMMING

Prof. ALİ OTO, MD, FESC, FACC, FHRS
Chairman, Department of Cardiology
Hacettepe University Faculty of Medicine, Ankara
Causes of “Non-response” after CRT

• Lack of Biventricular pacing
• Lack of optimal atrio-biventricular pacing
• Arrhythmias
  - AF
  - Frequent VPC’s
• Chronotropic incompetence
• Dyspnea of other causes
• Progression of the disease
• Patient selection
• Poor LV lead position

Need for periodic revision of program settings?
CAUSES OF NON-RESPONSE TO CRT

- Early Poor LV lead position
- Early Suboptimal device programming
- Late Disease progression
DON’T FORGET TO OPTIMISE DEVICE PROGRAMMING

• INITIAL PROGRAMMING
• PRE-HOSPITAL DISCHARGE MONITORING
• POST-DISCHARGE AND LONG-TERM FOLLOW-UP
Initial Programming of CRT Devices

- Selection of the pacing mode (VDD, DDD, DDDR, or VVIR),
- Lower and upper rate limits,
- The AV interval (to encourage a forced ventricular pacing including negative AV hysteresis)
- Anti-tachycardia therapy (CRT-D)
The basic pacing rate in CRT patients: the higher the better?

An increase in pacing rate from 40 to 70 bpm resulted in a stepwise augmentation of CO, however without affecting SV.

OPTIMISATION

- Programming of standard parameters
- AV interval optimization
  - Adjusts contraction sequence between LA and LV to optimize LV filling without truncating atrial contraction
- VV interval optimization
  - Adjusts contraction sequence between the left and right ventricles, ideally optimizing the left to produce the largest stroke volume

Optimization Techniques

- AV optimization
  - Echocardiography
    - Ritter method
    - Simplified inflow method
    - Iterative method
    - Maximal filling time
    - Mitral VTI
    - Aortic VTI
  - Finger plethysmography
  - Impedance cardiography
  - Device algorithms
    - PEA
    - AV EGM-based algorithm

- VV optimization
  - Echocardiography
    - Aortic VTI
    - TDI
  - Radionuclide ventriculography
    - LVEF
  - Finger plethysmography
  - Device algorithms
    - PEA

PEA = peak endocardial acceleration; VTI = velocity-time integral; TDI = tissue Doppler imaging.
GENERAL EVALUATION OF CRT AT FOLLOW-UP

- Ventricular fusion and pseudofusion on the ECG
- LV loss of capture: R/S < 1 in Lead V1, > 1 in Lead I
- Standard parameters should be controlled: Battery status, lead impedences and thresholds
- Rate histograms: Evaluation for rate adaptive pacing
- Causes for insufficient ventricular stimulation (< 90 %) (atrial tachyarrhythmias, frequent VPB’s, inap long AV delay, atr undersensing, ventricular oversensing)
GENERAL CONSIDERATION DURING FOLLOW-UP OF CRT PATIENTS

PROGRAMMING FEATURES

RATE RESPONSE SHOULD BE ACTIVATED IN Pts W CHRO INCOMP

TRACKING RATE SHOULD BE HIGH ENOUGH TO PERMIT BIV PACING

AMS SHOULD BE PROGRAMMED

SUFFICIENT SAFETY MARGIN IN OUTPUT PROGRAMMING TO ENSURE LV PACING

REFRACTORY PERIODS SHOULD BE ADJUSTED TO PREVENT PMT IN CASE OF FREQ VPC’s
AV DELAY OPTIMIZATION IN CRT PATIENTS

• OPTIMAL AV DELAY MAY BE HIGHLY VARIABLE BETWEEN SUBJECTS

• NEED FOR INDIVIDUAL OPTIMIZATION

• PARTICULARLY USEFUL IN PATIENTS WHO HAVE INTERATRIAL CONDUCTION DELAY AND WHO MAY REQUIRE LONG AV INTERVALS
Goals of AV Optimization

- Allow adequate time for passive filling of the ventricles
- Allow adequate time for a complete atrial contraction
  – atrial contribution to ventricular filling
- Allow efficient ventricular contraction

When AV timing is too short
– Ventricular filling time may be cut short
– The atrial kick can be cut short
– Hemodynamics can be impaired

If AV timing is too long, intrinsic ventricular activity can break
CRT Device Optimization with Echo

“Gold standard” of device timing optimization

- Stroke Volume (Aortic VTI)

- Trans-mitral Flow

- Intra-Ventricular Synchrony

- Aortic velocity time integral (VTI) for VV timing – RV and LV synchronization

- Mitral velocity Doppler echo is used for AV timing optimization – Sensed and paced AV delays
SHOULD AV DELAY BE OPTIMIZED?

<table>
<thead>
<tr>
<th>Data 3 months</th>
<th>AV Optimization (n = 20)</th>
<th>120 ms (n = 20)</th>
<th>VTI vs. 120</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA improvement (≥ 1 class)</td>
<td>75%</td>
<td>40%</td>
<td>P &lt; 0.03</td>
</tr>
<tr>
<td>QOL improvement</td>
<td>23 points</td>
<td>13 points</td>
<td>P &lt; 0.03</td>
</tr>
<tr>
<td>EF improvement</td>
<td>7.8%</td>
<td>3.4%</td>
<td>P &lt; 0.02</td>
</tr>
<tr>
<td>LVEDV change</td>
<td>–34 mL (P &lt; .05 baseline)</td>
<td>–20 mL (P = NS)</td>
<td>P = NS</td>
</tr>
</tbody>
</table>

Sawhney NS, Heart Rhythm 2004;1(5):562-7
SHOULD AV DELAY BE OPTIMIZED?

AV optimization improved clinical status vs. nominal settings

### Data 6 months

<table>
<thead>
<tr>
<th></th>
<th>Echo (n = 23)</th>
<th>120 ms (n = 15)</th>
<th>Echo vs. 120</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF</td>
<td>32.1%</td>
<td>27.5%</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>NYHA Class</td>
<td>2.1</td>
<td>3.0</td>
<td>P &lt; 0.01</td>
</tr>
</tbody>
</table>

### NYHA data 6 months

<table>
<thead>
<tr>
<th></th>
<th>Echo (n = 23)</th>
<th>120 ms (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Change</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Improved 1 Class</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Improved 2 Classes</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

Morales MA, PACE 2006;29:564-568
Transmitral flow AV delay optimization methods

- Iterative Method
- Ritter Method
- Simplified Mitral Inflow Method
• Measure the intrinsic PR; program the AV delay to a shorter value
• Using mitral velocity Doppler echo (MVDE), record and observe the E and A waves
• Shorten the AV delay in steps of 20 ms until obvious truncation of A wave is seen—the AV delay is too short
• Now step up the AV delay in 10 ms steps until you see E and A waves without A-wave cutoff (truncation) That point is the optimized AV delay
Short AV delay

- A-wave truncation limits atrial kick
AV Interval - 60 ms
AV Interval - 80 ms
AV Interval - 100 ms
Optimal AV Delay

Mitral Flow

Aortic Flow

Mitral valve closed

ECG

Echo

Ao
AV Interval - 110 ms
AV Interval - 120 ms
Long AV delay?

- No A-wave truncation
- E-A fusion
- Late ventricular contraction
AV Interval - 140 ms
AV Interval Optimization
Ritter Method

• AV intervals are programmed to a short and to a long value that does not truncate the A wave (e.g., 50 and 150 ms).

• The time interval between QRS onset and the end of the A wave (QA interval) measured at each setting.

• AV opt = AV long – (QA short – QA long)
Ritter Method - 50ms

154 msec
Ritter Method - 150ms

AV opt = AV long – (QA short – QA long)

AV opt = 150 – (154 – 128) = 124 msec

128 msec
AV Interval Optimization

Simplified Mitral Inflow Method

A long AV interval is programmed and the delay between the end of the A wave and the onset of mitral regurgitation (MR) is measured (t).

This value is then subtracted from long AV interval, yielding the optimal AV interval.

This approach relies on the presence of MR, which is a significant limitation.

Meluzin et al. PACE 2004;27:58–64
AV Interval Optimization
Simplified Mitral Inflow Method

200ms - 70 ms = 130 ms
Atrial Pacing Typically Requires Longer AV Delays

- Atrial pacing can create interatrial delay
- Atrial lead placement influences interatrial delay
  - Ideally, optimize the AVD for both sensing (As) and pacing (Ap)

\[ J \text{Interv Card Electrophysiol } 2002 \; 6:133-140 \]
\[ J \text{Cardiovas Electrophysiol} \; 2005;16:1273-1278 \]
\[ J \text{Cardiovasc Electrophysiol} \; 2007; 18:490-496 \]
Should we use the rate-adaptive AV delay in cardiac resynchronization therapy-pacing?

Christoph Melzer¹*, Hansjürgen Bondke¹, Thomas Körber², Christoph A. Nienaber², Gert Baumann¹, and Bruno Ismer²

¹The Medical Division, Charité University Medical Centre, Berlin, Germany; and ²The Rostock University Hospital, Clinic for Internal Medicine, Rostock, Germany

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Aims Recommendations for programming the rate-adaptive AV delay in CRT.

Methods and results In cases of continual biventricular pacing, the optimal AV delay in CRT (AVD_{opt}) is the net effect of the pacemaker-related interatrial conduction time (IACT), duration of the left-atrial electromechanical action (LA-EAC_{long}), and the duration of the left-ventricular latency period (SV-EAC_{short}). It can be calculated by \( AVD_{\text{opt}} = \text{IACT} + \text{LA-EAC}_{\text{long}} - \text{SV-EAC}_{\text{short}} \). We measured these three components in 20 CRT-ICD patients during rest and submaximal ergometric exercise (71 ± 9 W) resulting in a 22.5 ± 9.6 bpm rate increase. IACT and SV-EAC_{short} did not reveal significant differences. LA-EAC_{long}, however, varied significantly by −10.7 ± 16.1 ms (\( P = 0.008 \)) during exercise. In contrast to AVD_{optVDD}, there was a significant difference in AVD_{optDDD} of −8.8 ± 14.5 ms (\( P = 0.014 \)) between the resting and submaximal exercise conditions. In DDD pacing, AVD_{opt} was shortened by 2.6 ms/10 bpm.

Conclusion In consideration of the findings of the studies performed to date, the rate-adaptive AV delay should be deactivated.
Cardiac resynchronization therapy during rest and exercise: comparison of two optimization methods

Cinzia Valzania¹,²*, Maria J. Eriksson³,⁴, Giuseppe Boriani², and Fredrik Gadler¹,⁵

¹Department of Medicine, Division of Cardiology, Karolinska Institutet, Stockholm, Sweden; ²Institute of Cardiology, University of Bologna, Bologna, Italy; ³Department of Clinical Physiology, Karolinska University Hospital, Stockholm, Sweden; ⁴Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden; and ⁵Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden

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KEYWORDS
Cardiac resynchronization therapy; Optimization; Exercise; Echocardiography; Intracardiac electrogram

Aims Optimal exercise programming of cardiac resynchronization therapy (CRT) devices is unknown. We aimed to: (i) investigate variations in optimal atrioventricular (AV) and interventricular (VV) delays from rest to exercise, assessed by both echocardiography and an automated intracardiac electrogram (IEGM) method; (ii) evaluate the acute haemodynamic impact of CRT optimization performed during exercise.

Methods and results Twenty-four heart failure patients, previously implanted with a CRT defibrillator, underwent AV and VV delay optimization, by echocardiography and IEGM methods, both at rest and during supine bicycle exercise. Rest-to-exercise variations in optimal VV delay were observed in 58% of patients. Conversely, optimal AV delay did not change during exercise compared with rest. Substantial agreement of AV and VV delays was observed between both the optimization methods. Exercise optimization of VV delay by either method improved intraventricular dyssynchrony and increased aortic velocity time integral compared with the resting setting (P < 0.001).

Conclusion In patients implanted with a CRT device, optimal VV delay varied considerably from rest to exercise, while AV delay did not change. Re-assessment of the optimal pacing configuration during supine exercise, by echocardiography as well as IEGM methods, yielded an additional haemodynamic benefit to that provided by resting optimization.

Europace (2008) 10, 1161–1169
What is V-V Timing?

• A programmable interval that allows sequential or simultaneous biventricular activation (Programmable LV or RV first)

Why do we need V-V interval adjustment?

• V-V Timing programmability offers clinical flexibility for potential success in CRT optimization in HF patients since not all patients respond to simultaneous biventricular pacing
Synchronous vs Non-Synchronous BV Pacing: Is RV-LV Delay Important?

Systolic Function (Echo Index)

* $P<0.01$ vs. Simultaneous (s)

Why do we need VV interval Optimization?

- Both studies:
  - Single center study of consecutive patients with NYHA III/IV HF, QRS > 130 ms;
  - Trans-mitral flow optimized with AV delay post implant
  - N=22
  - VV delay of 0 for first 2 months.
  - Echo based optimization of VV delay (OPT) at 2 months.
- Sogaard, et al. Circ. 2002;106:2078-84
  - N=20
  - Optimal VV delay based on TDI
  - Acute data shown. After 3 mo., LVEF further improved to 38.6%. (P<0.01)

![Graph showing mean LVEF (%)](image)

* P<0.01 CRT with AV Opt versus Baseline
# P<0.01 VV Opt versus CRT with AV Opt
The data supporting ventricular optimization of biventricular pacing are limited to predominantly small, single centre, non-randomized, short-term studies employing various surrogate endpoints.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient number</th>
<th>Study design</th>
<th>Optimization method</th>
<th>Endpoints</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sogaard et al.</td>
<td>21</td>
<td>Non-randomized</td>
<td>Tissue tracking and derived global systolic contraction amplitude</td>
<td>LV dimension and function, 6 min walk test, and NYHA class</td>
<td>Further reduction in LVESV and improvement in global systolic contraction and LVEF. Improvement in NYHA class and 6 min walk distance at 3 months</td>
</tr>
<tr>
<td>Bordachar et al.</td>
<td>41</td>
<td>Non-randomized</td>
<td>Time to systolic velocity from tissue Doppler and longitudinal contraction from strain</td>
<td>LV dimension and function, NYHA class, 6 min walk test, and quality of life</td>
<td>Cardiac output, filling time, severity of MR, LVESV, LVEF, and inter-ventricular dyssynchrony improved by optimized biventricular pacing (six patients optimal on simultaneous setting). NYHA, quality of life, and 6 min walk distance improved at 3 months</td>
</tr>
<tr>
<td>Porciani et al.</td>
<td>21</td>
<td>Non-randomized</td>
<td>Myocardial performance index on echocardiogram</td>
<td>Myocardial performance index</td>
<td>Optimization of biventricular pacing further reduces MPI</td>
</tr>
<tr>
<td>Riedlbauchova et al.</td>
<td>19</td>
<td>Non-randomized</td>
<td>Stroke volume from aortic VTI</td>
<td>Aortic VTI</td>
<td>Biventricular pacing with LV pre-excitation better than RV pre-excitation</td>
</tr>
<tr>
<td>Vanderheyden et al.</td>
<td>20</td>
<td>Non-randomized</td>
<td>Time to peak systolic velocity on tissue Doppler and time to aortic and pulmonary valve opening</td>
<td>Aortic VTI and inter- and intra-ventricular dyssynchrony</td>
<td>Further increase in aortic VTI and filling time, and reduced inter- and intra-ventricular delay with optimized sequential biventricular pacing in 17/20 patients</td>
</tr>
</tbody>
</table>

Lim SH, Europace (2008) 10, 901–906
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Randomized/Non-randomized</th>
<th>Primary Outcome Measure</th>
<th>Secondary Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parreira et al.</td>
<td>15</td>
<td>Non-randomized</td>
<td>Time to peak systolic velocity on tissue Doppler</td>
<td>LVEF and ventricular dyssynchrony</td>
</tr>
<tr>
<td>Leon et al.</td>
<td>359</td>
<td>Non-randomized</td>
<td>Stroke volume from aortic VTI</td>
<td>NYHA class, 6 min walk test, and quality of life</td>
</tr>
<tr>
<td>Stockburger et al.</td>
<td>26</td>
<td>Non-randomized</td>
<td>PW Doppler of LV and RV ejection</td>
<td>Myocardial performance index</td>
</tr>
<tr>
<td>Boriani et al.</td>
<td>121</td>
<td>Randomized</td>
<td>Stroke volume from aortic VTI</td>
<td>6 min walk test, NYHA class, and quality of life</td>
</tr>
<tr>
<td>Phillips et al.</td>
<td>29</td>
<td>Non-randomized</td>
<td>Standard deviation of time to peak systolic velocity on tissue Doppler</td>
<td>Ventricular dyssynchrony (systolic dyssynchrony index)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Further significant increase in LVEF and reduction in electromechanical delay with sequential biventricular pacing</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>No significant difference in NYHA class or quality of life. Increased 6 min walk distance with optimized sequential biventricular pacing</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No significant difference with optimized sequential biventricular pacing (30% optimized to simultaneous biventricular pacing)</td>
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<tr>
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<td>Further reduction in ventricular dyssynchrony with optimized sequential biventricular pacing</td>
</tr>
</tbody>
</table>

Lim SH, Europace (2008) 10, 901–906
V-V delay optimization was associated
-with better immediate hemodynamic function than simultaneous biventricular stimulation,
-did not promote additional reverse remodeling at 6 Mos
-did not increase the proportion of echocardiographic responders to CRT
Echocardiographic techniques for LV-RV interval adjustment

– determination of stroke volume using the velocity time integral (VTI) across the LV outflow tract
– M Mode comparison of RV and LV lateral wall motion,
– Pulmonic outflow to LV outflow Doppler flow,
– Septal to posterior wall motion delay
– The frequency of delayed longitudinal contraction segments
VV-interval optimization was shown to determine a further benefit beyond CRT. A significant concordance was present between VV programming based on different echocardiographic methods.

*Bertini M, Echocardiography 2010;27:38-43*
RV > LV
10 msec
RV=LV
LV > RV
10 msec
LV > RV
20 msec
LV > RV
30 msec
LV>RV
40 msec
V-V INTERVAL OPTIMIZATION: Considerations

Despite conflicting results and a rather limited or moderate improvement in LV function or stroke volume VV optimization may prove beneficial in some patients with a suboptimal response to CRT in whom no cause is found.
Optimal AV and VV Delays Change Over Time with CRT

Change in AV and VV Delay Over Time

Optimal delay (Msec)

AV

V-V

Optimal A-V delay
Optimal V-V delay

Post Implant Visit Number

CRT implant 9 mos.

O’Donnell D. PACE 2005; 28:S24-S26
According to market research, on average, 41% of CRT patients are not “optimized”. Of these patients, 70% are optimized using echo methods. Only 33% of EP physicians “optimize” all of their CRT patients.

Base: n=98 Total Respondents
Source: Internal Market Research 2007
CRT Optimization Practices

There is no consensus regarding optimization strategies among EPs

AV Delay Optimization

- Optimize all patients: 40%
- Optimize only “non-responders”: 38%
- Some other strategy: 22%

VV Delay Optimization

- Optimize all patients: 33%
- Optimize only “non-responders”: 30%
- Some other strategy: 37%

Base: n=86 Total Respondents (AV Delay)

Base: n=84 Total Respondents (V-V Timing)

Source: Internal Market Research 2007
CONCLUSIONS

• Optimal device programming is the essential part of the CRT.

• As reverse remodelling and autonomic changes by biventricular pacing is a time dependent dynamic process; AV and VV status should be checked periodically.

• Don’t forget to optimize device programming! Particularly in sub-optimal response-