Cardiac Resynchronization Therapy – Newer Data on How to Increase Responders

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Cardiac resynchronization therapy (CRT) has been established as a valuable treatment option in certain subgroups of chronic heart failure patients. However, a consistent percentage of CRT recipients, about one third, are considered non-responders. Accumulating data support that targeted patient selection, proper left ventricular lead implantation and optimal device programming may enhance patient response to CRT. The present review addresses these issues from a practical perspective.

Cardiac resynchronization therapy (CRT) has earned its evidence-based credentials as a treatment option in certain subgroups of chronic heart failure patients. The indications of CRT in chronic heart failure patients under optimal medical treatment, with left ventricular (LV) ejection fraction (LVEF) \( \leq 35\% \) are presented in Table 1 (2013 guidelines of the European Society of Cardiology).\(^1\) Despite the fact that the majority of patients treated with CRT based on these recommendations present a favorable response, approximately one third are considered non-responders on the basis of several implemented criteria of clinical responsiveness.\(^2\)

A major caveat is the definition of response to CRT since several echocardiographic and clinical measures, such as mortality, hospitalizations, New York Heart Association (NYHA) class, quality of life, 6-minute walking test, exercise duration, maximal oxygen consumption (VO2 max), LV ejection fraction, LV dimensions have been used as surrogate markers of CRT response. However, a major challenge with profound clinical implications is to introduce and implement measures that maximize clinical response and thus enhance the benefit derived from this interventional and costly therapy.

Criteria and parameters that could affect response to CRT could be classified in: (A) Baseline characteristics, (B) Implantation criteria, (C) Optimal device programming.

**A. Baseline Characteristics**

QRS duration is the main pre-implantation factor which has been shown to have a major impact on the efficacy of CRT. Several metaanalyses have verified a...
Cleland et al. integrated several pre-implantation variables predictive of CRT response (age, sex, NYHA class, etiology, QRS morphology, QRS duration, LV ejection fraction and systolic blood pressure) in a multivariate model and showed that only QRS duration was a significant predictor of the CRT effect on patient outcome, with an increasing benefit with prolonged QRS duration. The authors reported that a critical value of QRS duration of 140 ms confers a high certainty of favorable response. It should also be noted that CRT has not been shown to provide any benefit in patients with QRS less than 120 ms even in the presence of echocardiographically-documented mechanical dyssynchrony. Furthermore, in the recently reported EchoCRT study, the use of CRT in NYHA class III-IV heart failure patients (LVEF ≤35%) with QRS duration less than 130 ms was also associated with an excess mortality due to a significant increase in the rate of death from cardiovascular causes. Therefore, based on the existing state of evidence a QRS duration less than 120 ms represents a contraindication for CRT therapy.

Apart from QRS duration, several other preimplantation characteristics have been related to a favorable response to CRT. Secondary analyses from randomized trials have shown that female gender, presence of left bundle branch block (LBBB) morphology, non-ischemic cardiomyopathy, are predictors of significant clinical benefit from CRT. In a subanalysis of MADIT-CRT, Hsu et al identified the following specific predictors of “super-response” to CRT as evidenced by near-normalization of LVEF: female gender, no prior myocardial infarction, QRS duration ≥150 ms, presence of LBBB, body mass index <30 kg/m², and smaller baseline

**Table 1.** Class of recommendation and level of evidence (LoE) for cardiac resynchronization therapy (CRT) in patients with chronic heart failure and LVEF ≤35% despite adequate medical treatment.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>LoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBBB – NYHA class II, III, ambulatory IV - QRS &gt;150 ms</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>LBBB – NYHA class II, III, ambulatory IV - QRS 120 - 150 ms</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Non-LBBB - NYHA class II, III, ambulatory IV - QRS &gt;150 ms</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Non-LBBB – NYHA class II, III, ambulatory IV - QRS 120 - 150 ms</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>QRS duration &lt;120 ms</td>
<td>III</td>
<td>B</td>
</tr>
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**Patients in permanent atrial fibrillation**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>LoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRS ≥120 ms - NYHA class III, ambulatory IV (biventricular pacing as close to 100% as possible can be achieved)</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>

Patients with reduced LVEF who are candidates for AV junction ablation due to uncontrolled heart rate

**AV** = atrioventricular; **LBBB** = left bundle branch block, **LVEF** = left ventricular ejection fraction, **NYHA** = New York Heart Association.

**Figure 1.** Schematic classification of variables that may enhance response to cardiac resynchronization therapy (CRT).
left ventricular left atrial volume index.11 The preimplanta-
tion assessment of scar burden may also prove useful in the
identification of CRT candidates that may respond to CRT.
Several studies have shown that an increased myocardial scar
burden, assessed either by single-photon emission computed
tomography (SPECT) or magnetic resonance imaging, is an
independent predictor of patient outcome following CRT.12-14
Additionally, inotropic contractile reserve during dobutamine
stress echocardiography has been shown to predict response
to CRT, by functionally differentiating viable myocardium
from scar tissue on the basis of displayed inotropic response.15

The predictive value of echocardiographically-verified me-
chanical dyssynchrony for selection of optimal candidates for
CRT has not been clarified. Several single-center studies have
reported a significant correlation between echocardiographic
measures of mechanical dyssynchrony and clinical response
to CRT.16-18 However, in the large-scale, prospective, multicenter
PROSPECT trial, all twelve evaluated echocardiographic
measures of dyssynchrony demonstrated a modest sensitivity,
specificity and accuracy to predict response to CRT.19 There-
fore, based on the existing evidence, noninvasive imaging
should not be integrated in decision formulating algorithms
for selection of optimal candidates for CRT.1

B. IMPLANTATION CRITERIA

Conceptually, CRT is expected to have the maximal ben-
eficial effect on patient outcome, when the LV lead is placed
at the segment displaying maximal electromechanical delay,
thus enabling correction of dyssynchrony during biventricular
pacing. Accumulating evidence suggests that the location and
electrophysiological characteristics of the LV lead location may
have an impact on outcome of CRT recipients. Therefore, the
identification and targeting of favorable sites during LV lead
implantation may increase clinical response to CRT.

Optimal lead location could be classified along the short
axis (anterior vs lateral vs posterior segments) as well as along
the longitudinal axis (basal vs mid vs apical segments). Singh et
al showed that apical location of the LV lead is associated with
higher incidence of heart failure or death as compared to all
other LV lead locations.20 The detrimental effect of LV apical
pacing has been validated in other single-center studies and is
partly due to reduced interelectrode distance and pacing of a
region with less delayed electromechanical delay.20-21 On the
other hand, there are conflicting data in the literature regard-
ing the optimal pacing location in the short axis. Older studies
have suggested that LV lead placement in a posterolateral or
lateral coronary sinus branch is associated with significantly in-
creased CRT benefit as compared to anterior lead location.22,23
A prespecified substudy of the REVERSE trial demonstrated
a more favorable outcome of CRT recipients when the LV
lead was implanted at a lateral as compared to non-lateral

site.24 However, in secondary analyses of the COMPANION
and MADIT-CRT trials, LV lead location along the short axis
(anterior vs lateral vs posterior wall) had no significant effect
on the rate of heart failure hospitalization or mortality.20,25

Several studies have also shown the importance of an
individualized approach in selection of the optimal pacing
site by targeting the most delayed segment, avoiding areas of
myocardial scar.26,27 In a prospective study, targeted LV
lead placement at the echocardiographically identified most
delayed viable site was associated with significantly improved
clinical response, reverse remodeling and reduced rate of
death and heart failure-related hospitalization as compared
to a standard approach.28 However, it should be acknowledged
that implantation of the LV lead at a specific targeted segment
is not feasible in a considerable percentage of implantations
due to limitations related to coronary venous anatomy, phrenic
erve stimulation, inadequate lead stability and suboptimal
pacing threshold.

Another implantation factor that can be useful to select
the optimal LV lead implantation site and predict anticipated
benefit from CRT is the intraoperative assessment of electro-
cal dyssynchrony and the degree of delayed activation at the
pacing site. The latter can be measured from QRS onset to
LV ventricular electrogam (QLV) at the site of implanta-
tion.29 Several studies have shown that longer electrical delay
at the LV implantation site is strongly and independently as-
associated with reverse remodeling among CRT recipients.29,30
From a practical point of view, it has been proposed to select
intraoperatively pacing sites with a QLV higher than 95 ms,
since lower values are associated with poor patient outcome.29

C. OPTIMAL DEVICE PROGRAMMING

The two basic goals of cardiac resynchronization program-
mong are (a) to maximize biventricular pacing percentage and
(b) to program the atrioventricular (AV) and interventricular
(VV) delay settings to enhance AV and VV resynchronization.
Several studies have shown that maximal mortality benefit by
CRT is achieved with biventricular pacing percentages exceed-
ing 98% of all ventricular beats. Thus, avoidance of native AV
conduction is of primary importance.31 In this context, a low
threshold should be maintained for referring CRT recipients
with chronic atrial fibrillation for AV node ablation. Program-
mong tips, methods and algorithms that can be helpful in car-
diac resynchronization programming are presented in Table 2.

Regarding optimization of AV and VV intervals, several
device-based algorithms have been introduced to identify
patient-specific, optimal values of AV and VV intervals. How-
ever, based on the results of the SMART-AV study, neither
echocardiographically optimized AV delay, nor AV delay
optimized by the algorithm SmartDelay provided incremental
benefit in CRT patients as compared to fixed AV delay of
Tips to avoid loss of resynchronization due to functional atrial undersensing
- Disable PVARP extension after PVC
- Avoid atrial undersensing
- Avoid R wave double counting

Activate algorithms to promote continuous tracking
- Algorithms that shorten the PVARP: Atrial Tracking Recovery™ (Medtronic), Tracking PreferenceT™ (Boston Scientific)
- Algorithms that shorten the AV interval following sensed ventricular events: Negative AV hysteresis (St. Jude Medical)

Activate algorithms to promote resynchronization during ventricular ectopy or conducted atrial fibrillation
- Triggered ventricular pacing following ventricular sensed event: Ventricular Sense Response™ (Medtronic), Biventricular Trigger (Boston Scientific), BiV with RVsense (Biotronik)
- Ventricular rate regularization (Boston Scientific)

Table 2. Tips and algorithms in cardiac resynchronization therapy (CRT) programming

<table>
<thead>
<tr>
<th>Tips</th>
<th>Algorithms</th>
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<tbody>
<tr>
<td>In CRT patients with intact AV conduction, the upper rate limit should be programmed faster than the maximum sinus rate to avoid loss of biventricular pacing during exercise.</td>
<td>Activate algorithms to promote continuous tracking: Atrial Tracking Recovery™ (Medtronic), Tracking PreferenceT™ (Boston Scientific).</td>
</tr>
<tr>
<td>Tips to avoid loss of resynchronization due to functional atrial undersensing</td>
<td>Activate algorithms to promote resynchronization during ventricular ectopy or conducted atrial fibrillation: Ventricular Sense Response™ (Medtronic), Biventricular Trigger (Boston Scientific), BiV with RVsense (Biotronik).</td>
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<tr>
<td>120 ms. Additional studies have validated the limited role of routine AV and VV delay optimization in all CRT recipients. Thus, it seems prudent to initially select an AV delay of 100-120 ms with simultaneous biventricular pacing, sparing echo-guided or device algorithm-based AV and VV optimization only for non-responders.</td>
<td>Table 2. Tips and algorithms in cardiac resynchronization therapy (CRT) programming.</td>
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</table>

**Conclusion**

Numerous factors may influence clinical response to CRT. The benefit derived by this interventional treatment can be maximized if all the above-mentioned criteria related to patient selection, implantation techniques, patient follow-up and device programming are taken into consideration. Greatest benefit appears to be derived by selecting patients in sinus rhythm, with LBBB morphology on the electrocardiogram and a QRS duration of >150 ms, placing the LV lead in a posterolateral position away from scarred myocardial tissue, and optimally programming the device.

**References**

24. Thibault C, Donal E, Meunier C, et al. Sites of left and right ventricular lead implantation and response to cardiac resynchronization therapy observations from the REVERSE trial. *Eur Heart J* 2012; 33:2662-2671.