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REVIEW

Cardiac Resynchronization Therapy – Newer Data on How to Increase Responders

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ABSTRACT

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 optical medical treatment, with left ventricular (LV) ejection fraction (LVEF) ≤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.

ABBREVIATIONS
AV = atrioventricular
CRT = cardiac resynchronization therapy
LBBB = left bundle branch block
LV = left ventric-le(-ular)
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association
VO2 max = maximal oxygen consumption
VV = interventricular

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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

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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.

Patients in sinus rhythm		
Recommendations	**Class**	**LoE**
LBBB – NYHA class II, III, ambulatory IV - QRS >150 ms	I	A
LBBB – NYHA class II, III, ambulatory IV - QRS 120 - 150 ms	I	B
Non-LBBB - NYHA class II, III, ambulatory IV - QRS > 150 ms	IIa	B
Non-LBBB – NYHA class II, III, ambulatory IV - QRS 120 - 150 ms	IIb	B
QRS duration <120 ms	III	B
Patients in permanent atrial fibrillation		
Recommendations	**Class**	**LoE**
QRS ≥120 ms - NYHA class III, ambulatory IV (biventricular pacing as close to 100% as possible can be achieved)	IIa	B
Patients with reduced LVEF who are candidates for AV junction ablation due to uncontrolled heart rate	IIa	B

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

significant CRT benefit in patients with QRS ≥150 msec.[3,4] 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.[5] 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.[6] 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.[7] 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,[8] presence of left bundle branch block (LBBB) morphology,[9] non-ischemic cardiomyopathy,[10] 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/m^2, and smaller baseline

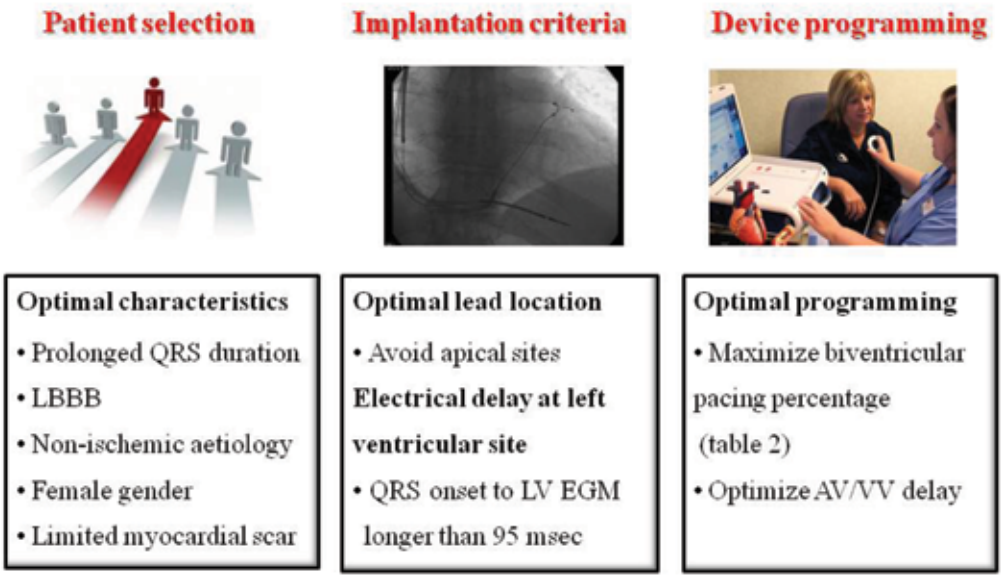

FIGURE 1. Schematic classification of variables that may enhance response to cardiac resynchronization therapy (CRT).

left ventricular left atrial volume index.[11] The preimplantation 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 mechanical 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] Therefore, 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 beneficial 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 regarding 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 increased 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 nerve 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 electrical 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 implantation.[29] Several studies have shown that longer electrical delay at the LV implantation site is strongly and independently 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 programming 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 exceeding 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. Programming tips, methods and algorithms that can be helpful in cardiac 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. However, 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

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

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
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)

CRT = cardiac resynchronization therapy, PVARP = post-ventricular atrial refractory period, PVC = premature ventricular contraction, AV = atrioventricular

120 ms.[32] Additional studies have validated the limited role of routine AV and VV delay optimization in all CRT recipients.[1] 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.[1]

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

1. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resychronization therapy of the European Society of Cardiology (ESC). *Europace* 2013; 15:1070-1118.
2. McAlister FA, Ezekowitz J, Hooton N, et al. Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction: a systematic review. *JAMA* 2007;297:2502-2514.
3. Stavrakis S, Lazzara R, Thadani U. The benefit of cardiac resynchronization therapy and QRS duration: a meta-analysis. *J Cardiovasc Electrophysiol* 2012; 23:163-168.
4. Sipahi I, Carrigan TP, Rowland DY, et al. Impact of QRS duration on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. *Arch Intern Med* 2011; 171:1454-1462.
5. Cleland JG, Abraham WT, Linde C, et al. An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure. *Eur Heart J* 2013; 34:3547-3556.
6. Beshai JF, Grimm RA, Nagueh SF, et al. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. *N Engl J Med* 2007; 357:2461-2471.
7. Ruschitzka F, Abraham WT, Singh JP, et al. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. *N Engl J Med* 2013; 369:1395-1405.
8. Arshad A, Moss AJ, Foster E, et al. Cardiac resynchronization therapy is more effective in women than in men: the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) trial. *J Am Coll Cardiol* 2011; 57:813-820.
9. Zareba W, Klein H, Cygankiewicz I, et al. Effectiveness of cardiac resynchronization therapy by QRS morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). *Circulation* 2011; 123:1061-1072.
10. Bilchick KC, Kamath S, DiMarco JP, et al. Bundle-branch block morphology and other predictors of outcome after cardiac resynchronization therapy in Medicare patients. *Circulation* 2010; 122:2022-2030.
11. Hsu JC, Solomon SD, Bourgoun M, et al. Predictors of super-response to cardiac resynchronization therapy and associated improvement in clinical outcome: the MADIT-CRT study. *J Am Coll Cardiol* 2012; 59:2366-2373.
12. Adelstein EC, Tanaka H, Soman P, et al. Impact of scar burden by single-photon emission computed tomography myocardial perfusion imaging on patient outcomes following cardiac resynchronization therapy. *Eur Heart J* 2011; 32:93-103.
13. White JA, Yee R, Yuan X, et al. Delayed enhancement magnetic resonance imaging predicts response to cardiac resynchronization therapy in patients with intraventricular dyssynchrony *J Am Coll Cardiol* 2006;48:1953-1960.
14. Cochet H, Denis A, Ploux S, et al. Pre- and intra-procedural predictors of reverse remodeling after cardiac resynchroni-

zation therapy: an MRI study. *J Cardiovasc Electrophysiol* 2013;24:682-691.
15. Aggeli C, Poulidakis E, Felekos I, et al. Prognostic value of inotropic contractile reserve during low-dose dobutamine stress echo in identifying CRT responders. *Eur J Echocardiogr* 2011; 12 (suppl2): ii67 (Abst)
16. Bax JJ, Bleeker GB, Marwick TH, et al. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. *J Am Coll Cardiol* 2004; 44:1834-1840.
17. Yu CM, Fung JW, Zhang Q, et al. Tissue Doppler imaging is superior to strain rate imaging and postsystolic shortening on the prediction of reverse remodeling in both ischemic and nonischemic heart failure after cardiac resynchronization therapy. *Circulation* 2004; 110:66-73.
18. Sogaard P, Egeblad H, Kim WY, et al. Tissue Doppler imaging predicts improved systolic performance and reversed left ventricular remodeling during long-term cardiac resynchronization therapy. *J Am Coll Cardiol* 2002; 40:723-730.
19. Chung ES, Leon AR, Tavazzi L, et al. Results of the Predictors of Response to CRT (PROSPECT) trial. *Circulation* 2008; 117:2608-2616.
20. Singh JP, Klein HU, Huang DT, et al. Left ventricular lead position and clinical outcome in the multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT) trial. *Circulation* 2011; 123:1159-1166.
21. Merchant FM, Heist EK, McCarty D, et al. Impact of segmental left ventricle lead position on cardiac resynchronization therapy outcomes. *Heart Rhythm* 2010; 7:639-644.
22. Rossillo A, Verma A, Saad EB, et al. Impact of coronary sinus lead position on biventricular pacing: mortality and echocardiographic evaluation during long-term follow-up. *J Cardiovasc Electrophysiol* 2004; 15:1120-1125.
23. Butter C, Auricchio A, Stellbrink C, et al. Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients. *Circulation* 2001; 104:3026-3029.
24. Thιbault 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.
25. Saxon LA, Olshansky B, Volosin K, et al. Influence of ventricular lead location on outcomes in the COMPANION study. *J Cardiovasc Electrophysiol* 2009; 20: 764-768.
26. Derval N, Steendijk P, Gula LJ, et al. Optimizing hemodynamics in heart failure patients by systematic screening of left ventricular pacing sites: the lateral left ventricular wall and the coronary sinus are rarely the best sites. *J Am Coll Cardiol* 2010; 55:566-575.
27. Delgado V, van Bommel RJ, Bertini M, et al. Relative merits of left ventricular dyssynchrony, left ventricular lead position, and myocardial scar to predict long-term survival of ischemic heart failure patients undergoing cardiac resynchronization therapy. *Circulation* 2011; 123:70-78.
28. Khan FZ, Virdee MS, Palmer CR, et al. Targeted left ventricular lead placement to guide cardiac resynchronization therapy: the TARGET study: a randomized controlled trial. *J Am Coll Cardiol* 2012; 59:1509-1518.
29. Gold MR, Birgersdotter-Green U, Singh JP, et al. The relationship between ventricular electrical delay and left ventricular remodeling with cardiac resynchronization therapy. *Eur Heart J* 2011; 32:2516-2524.
30. Singh JP, Fan D, Heist EK, et al. Left ventricular lead electrical delay predicts response to cardiac resynchronization therapy. *Heart Rhythm* 2006; 3:1285-1292.
31. Hayes DL, Boehmer JP, Day JD, et al. Cardiac resynchronization therapy and the relationship of percent biventricular pacing to symptoms and survival. *Heart Rhythm* 2011; 8:1469-1475.
32. Ellenbogen KA, Gold MR, Meyer TE, et al. Primary results from the SmartDelay determined AV optimization: a comparison to other AV delay methods used in cardiac resynchronization therapy (SMART-AV) trial. A randomized trial comparing empirical, echocardiography-guided, and algorithmic atrioventricular delay programming in cardiac resynchronization therapy. *Circulation* 2010; 122:2660-2668.