Cardiac Resynchronization Therapy
How to Decrease Nonresponders

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KEYWORDS

• Cardiac resynchronization therapy • Nonresponders • Heart failure

KEY POINTS

- Nonresponse to cardiac resynchronization therapy (CRT) therapy is still a major issue in therapy expansion.
- The description of fast, simple, cost-effective methods to optimize CRT could help in adapting pacing intervals to individual patients.
- A better understanding about the importance of appropriate patient selection, left ventricular lead placement, and device programming, together with a multidisciplinary approach and an optimal follow-up of the patients, may reduce the percentage of nonresponders.

BACKGROUND

Cardiac resynchronization therapy (CRT) in appropriately selected heart failure (HF) patients has been shown to induce left ventricular (LV) reverse remodeling and improve both functional capacity and quality of life, thus decreasing hospital admissions and mortality.[1] However, current CRT indications cover a broad spectrum of patients. Although CRT will improve symptoms and survival in most patients, about one-third (30%) of CRT recipients do not obtain clinical benefit from the therapy and are considered clinical nonresponders. The percentage reaches 40% when the criterion is echocardiographic response to CRT, defined as significant LV reverse remodeling.[2]

CRITERIA FOR RESPONSE TO CARDIAC RESYNCHRONIZATION THERAPY

To define clinical response, a rather imprecise criterion (improvement in New York Heart Association [NYHA] functional class) has been extensively used; more objective criteria, such as 10% or more increased distance in the 6-minute walking test, also have been applied. Several randomized studies have demonstrated the beneficial effects of CRT for patients in NYHA class III or ambulatory class IV, and more recently, in mild HF (class II with systolic dysfunction), and the indication for CRT has now been extended to patients in NYHA class II.[1] Patients with mild HF show less improvement in functional capacity, because it is already acceptable[3]; however, they clearly show LV remodeling. On the other hand, the magnitude of change in the left ventricular end-systolic volume has been correlated with a better survival rate and fewer hospital admissions.[4] Therefore, in class II patients, LV remodeling is a good marker of response.

FACTORS THAT MAY IMPROVE THE NUMBERS OF CARDIAC RESYNCHRONIZATION THERAPY RESPONDERS

The lack of response to CRT depends on multiple factors, starting with appropriate patient selection,

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followed by factors related to the implant procedure and to optimization of therapy, including appropriate drugs and programming, during follow-up (Fig. 1).

Patient Selection

Since the advent of CRT, numerous factors have been related to the success of the therapy. Several clinical and image-related characteristics help to identify patients with low probability to benefit from therapy. Improved patient selection using these important markers of response or nonresponse may reduce inappropriate indications, avoiding unnecessary patient risks and saving the costs associated with the therapy.

QRS morphology

Although patients with left bundle branch block (LBBB) clearly benefit from CRT, patients with wide QRS but right bundle branch block (RBBB) have a different activation pattern. Fewer than 25% of patients with RBBB demonstrated LV activation delay equivalent to LBBB results.[5] CRT was less effective in improving hemodynamics in an animal model of RBBB,[6] and recent clinical data from the MADIT-CRT[7] and RAFT[8] trials failed to demonstrate a reduction in hospital admissions and deaths in patients with RBBB treated with CRT.[9]

Subgroup analyses based on QRS morphology in the main randomized trials of CRT suggest that patients with complete LBBB (Fig. 2) receive greater benefit from CRT, compared with patients with nonspecific intraventricular conduction delay or with RBBB.[1]

QRS width

The lack of CRT benefit in patients with narrow QRS (<120 ms) is now widely accepted.[1] Most of the main randomized clinical trials included patients with wide QRS defined as QRS greater than 120 or 130 ms. However, a large meta-analysis did not report a significant reduction in death and hospital admissions in patients treated with CRT who had a QRS of 120 to 149 ms, whereas CRT was more effective in reducing adverse clinical events in those patients with a QRS duration greater than 150 ms.[10] LV reverse remodeling and clinical responses increase progressively with increasing baseline QRS duration, but mainly in those patients with LBBB morphology.[11]

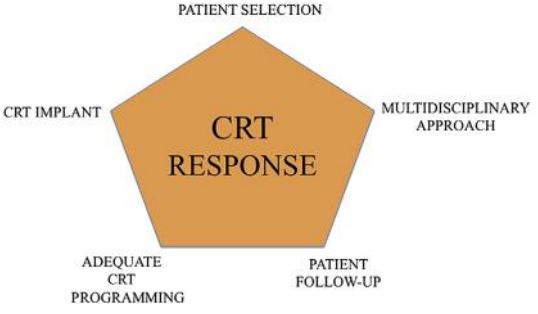

Fig. 1. Factors that could affect the response to CRT.

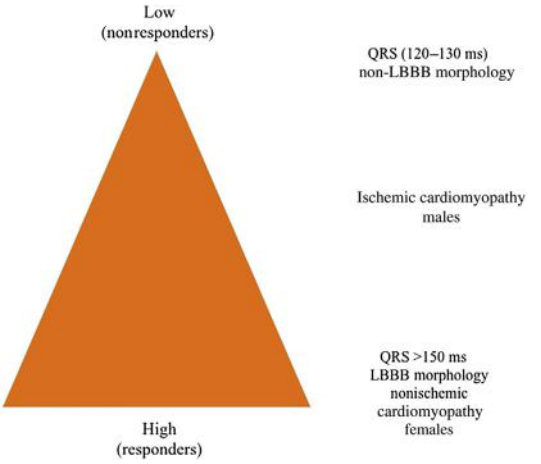

Fig. 2. Clinical factors and probability of response to CRT. (*Adapted from* Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J 2013;34(29):2302; with permission.)

Heart failure cause

Patients with ischemic cardiomyopathy tend to have a poor response to CRT and show less improvement in LV reverse remodeling and left ventricular ejection fraction (LVEF).[12,13] The extent of myocardial scar tissue may be one of the key determinants of the poor response in these patients because slow conduction across the scar areas may reduce the efficacy of the therapy.[14]

On the other hand, the existence of large scar areas also limits the LV reverse remodeling.[15] It is likely that CRT mitigates the deleterious effects of dyssynchrony induced by the LBBB but cannot increase the contractility of necrotic areas (Fig. 3).

Gender differences

Subanalyses from randomized clinical trials and meta-analyses describe greater reductions in the risk of death or hospitalizations in women than in men. The degree of reverse cardiac remodeling also tended to be greater in women than in men.[16,17]

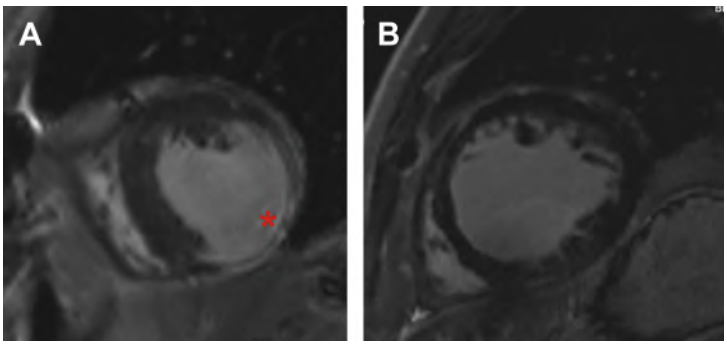

Fig. 3. cMRI axial view. (*A*) Dilated cardiomyopathy with a large posterolateral transmural scar (*red asterisk*). (*B*) Dilated cardiomyopathy without scar.

Men and women with HF are known to differ in comorbidities, risk factors, and response to medical treatment. Women had more nonischemic cause and LBBB morphology that has been associated with better CRT outcomes, compared with men. Moreover, women with dilated cardiomyopathy usually had less myocardial scar than their male counterparts.[18]

Atrial fibrillation

About 30% of patients with advanced HF will develop atrial fibrillation (AF). The prevalence of AF is directly related to worsening NYHA functional class.[19] However, despite the high prevalence of AF in CRT candidates, only 2% of the patients included in the main randomized trials were in AF.[1] Despite the lack of randomized studies in patients with AF, 23% of patients who received a CRT in Europe were in AF.[20]

In a meta-analysis that included 7945 patients from 33 observational studies, Wilton and colleagues[21] found that the 22% of patients in AF had a higher mortality and a greater risk of nonresponse to CRT than patients in sinus rhythm. Patients in AF have fast and irregular ventricular rates, which may interfere with complete biventricular pacing delivery. Therefore, strict control of the intrinsic heart rate is required in AF patients in order to achieve the maximum percentage of ventricular pacing.

Based on observational studies, some investigators[22] recommend systematic atrioventricular junction (AVJ) ablation in these patients to ensure 100% capture by pacing, while others support a conservative initial strategy, optimizing the medical treatment and programming the device to obtain a high percentage of ventricular pacing, and recommend reserving AVJ ablation only for patients with poor heart rate control.[23–26] Randomized trials may clarify the best strategy to follow in these patients.

Clinical parameters and comorbidities

Many clinical parameters and comorbidities help to identify patients with low probability of response and an increased mortality risk. Numerous studies have found that a highly dilated left ventricle and severe mitral regurgitation indicate a lower probability of response.[12–28] Patients with very advanced disease have likely reached a point of no return and CRT may not reverse or stabilize HF in these patients.

The presence of multiple predictors of lower response and increased mortality has an additive effect.[29–33] Recently, the EAARN score,–an algorithm to calculate the risk of mortality in patients treated with CRT, has been reported. The score is based on preimplant risk factors (LVEF <22%; age $\geq$70 years, AF, renal dysfunction, and basal NYHA functional class IV).[34] The EAARN score demonstrated an excellent prognosis and low mortality in patients with 0 to 1 risk factors, whereas those patients with 3 risk factors or more had a high mortality despite the benefits of the therapy. Overall mortality was 21.4 per 100 person-years in the subgroup of patients with an EAARN score 3 or greater, compared with 7 per 100 person-years with an EAARN score of 0 or 1 (hazard ratio [HR] 4.04; confidence interval [CI] 95% 2.9–6.5, *P*<.001). This finding highlights the need to start CRT therapy at the earliest stages of the disease, avoiding unnecessary delay that could compromise response and survival.

Imaging as a tool for patient selection

The use of echocardiography to assess mechanical dyssynchrony and select patients for CRT has not yet been standardized. Many observational studies have shown that the presence of LV dyssynchrony is associated with an improvement in CRT response; nevertheless, these results were not supported by the large, multicenter, PROSPECT study. The echocardiographic parameters tested in that trial failed to predict the response to therapy with accuracy.[35]

Selection of patients for CRT based on LV mechanical dyssynchrony assessed with imaging techniques is not routinely recommended as a

selection criterion for CRT.[1] One of the reasons to explain the lack of usefulness of echocardiographic methods is the complexity and heterogeneity of the parameters. A recent study has shown that when any of 4 simple criteria for dyssynchrony were present (septal flash, atrioventricular [AV] dyssynchrony, exaggerated right ventricular [RV]-LV response), the probability of response was high. The investigators suggest that CRT may only work when a correctable mechanism is present, and this mechanism can be identified by simple echocardiographic measurements.[36]

Although preimplant cardiac MRI (cMRI) is still uncommon in most practices, some studies have shown its benefit in assessing dyssynchrony and scar burden. Pacing in regions of scar detected by delayed enhancement MRI predicts lack of response to CRT.[15,37] Moreover, the presence, size, and heterogeneity of myocardial scar identified by cMRI predict appropriate ICD therapies in patients treated with CRT and may allow the identification of patients with a low risk of sudden cardiac death.[38] Large, randomized trials are needed to evaluate the use of cMRI in selecting patients for CRT.

Cardiac Resynchronization Therapy Implant Procedure, Left Ventricular Lead Localization, and Type of Leads

Lack of response to CRT is sometimes related to an inappropriate LV lead location. In one study that reviewed the reasons for lack of CRT response, suboptimal LV lead position was implicated in 21% of the patients.[39] Along with correct patient selection, the location of the LV lead also could improve the response to therapy.

Lead localization

In the absence of additional information regarding activation sequence, the greatest delay in mechanical contraction in patients with LBBB is frequently located in the LV posterolateral region. The REVERSE study showed that a lateral LV lead position was associated with better outcomes, in comparison with other locations.[40] On the other hand, data from the MADIT CRT trial demonstrated that an LV lead location in basal or midventricular positions was superior to apical positions. In that trial, LV apical lead position was associated with increased risk of HF (HR 1.72; 95% CI 1.09–2.71) and death (HR 2.91; 95% CI 1.42–5.97).[41]

The existence of individual variations in the conduction delay and the presence of myocardial scar may modify the site of latest activation. The TARGET trial randomized 220 HF patients to an LV nonapical position coincident with the latest activated areas (assessed with speckle-tracking echocardiography) or to a standard unguided LV lead position.[42] The first group had a greater proportion of clinical and echocardiographic responders at 6-month follow-up.

Knowledge of LV viability, scar distribution, and contraction patterns provided by MRI or echocardiography may help to optimize the LV lead position. In these cases, the use of myocardial imaging may individualize CRT and could help to place the LV in a vein adjacent to the latest activated region far away from the scar.[15–26,28–37]

Type of left ventricular lead

There is a great variability in coronary venous anatomy that complicates the placement of the LV lead in a target position. The standard bipolar leads have high rates of LV lead dislodgement, phrenic nerve stimulation, loss of capture, and increased LV pacing thresholds. The recent development of LV leads with different diameters and shapes may facilitate the placement of the lead in a correct position. One of the best advances in LV leads is the design of quadripolar leads, with 4 independent electrodes that allow the programming of additional vectors for LV pacing. Altogether, it is now easier to find a stable LV position with low pacing thresholds, minimizing the incidence of phrenic nerve stimulation.[43]

Recently, a single-center observational study described a lower rate of hospitalizations for HF and LV lead surgical revision in patients with quadripolar LV leads. The use of quadripolar leads facilitates targeting pacing at more proximal regions of the coronary venous branches, maintaining a more distal and stable lead position.[44]

Moreover, quadripolar leads enable multipoint pacing. This technology delivers 2 LV pulses from a single quadripolar lead (MultiPoint Pacing; St Jude Medical, Minneapolis, MN, USA). Early studies show promising results by improving hemodynamics and the rate of response to CRT.[45,46] However, the link between acute hemodynamic measures and long-term outcome is not yet proven. Whether multipoint pacing will translate into long-term clinical benefits remains unknown and will require testing in large randomized trials.[47]

Cardiac resynchronization therapy device optimization

Echocardiography has traditionally been considered the gold standard for CRT optimization. However, these methods include complex adjustments that require expertise and are time-consuming. Moreover, current literature suggests that routine

AV and interventricular (VV) delay optimization have no effect on CRT outcomes[48]; therefore, routine CRT optimization is not recommended in these patients.[1]

On the other hand, suboptimal programming of the AV or VV delays may limit the response to CRT. Therefore, optimization of the AV and VV intervals may be recommended to correct suboptimal device settings.[19]

Despite the lack of strong evidence in favor of optimization, many individual examples demonstrate the possibility to strongly improve response. Therefore, the description of fast, simple, cost-effective methods to optimize CRT could help in adapting pacing intervals to individual patients. In efforts to simplify CRT optimization, some automatic optimization algorithms based on intracardiac electrograms have been implemented, with conflicting results.[49–51]

Previous studies have linked QRS shortening to clinical response and echocardiographic improvement.[52,53] Therefore, shortening the paced QRS duration could be a simple and widely applicable optimization method.

The authors recently described a simple method of QRS-based optimization that is called fusion-optimized intervals (FOI), which uses fusion with intrinsic conduction to achieve the shortest possible QRS.[54] The idea behind fusion-guided biventricular pacing with the intrinsic rhythm is to allow partial or complete intrinsic depolarization of the VV septum (fusion pacing), which creates 3 activation fronts instead of 2 during pure biventricular pacing.

The FOI method is feasible and simple and can be easily performed after the implant. This method reduces the paced QRS duration and improves the acute hemodynamic response in comparison to nominal programming of the device.

The Medtronic Adaptive CRT algorithm uses intrinsic intervals to provide RV-synchronized LV pacing when AV conduction is normal, or biventricular pacing otherwise. A recent randomized study that evaluated this algorithm demonstrated that pacing with LV fusion was equivalent to echocardiographic optimization.[51–55]

Device Programming

Sustained and effective biventricular pacing is necessary to achieve response to CRT. Koplan and colleagues[56] demonstrated a 44% reduction in the composite end point of mortality and HF hospitalization in patients receiving 93% to 100% of biventricular pacing, compared with those receiving 92% or less. These results were reinforced by the published results of a series of 36,935 patients, showing the greatest reduction in mortality in patients with biventricular pacing greater than 98%.[57]

The main causes for lost ventricular pacing in patients treated with CRT were inappropriately long AV interval delay (34%) and atrial tachycardia, mainly AF (31%) or premature ventricular beats (17%).[58] Therefore, a great effort should be made to reach 100% of ventricular pacing, including aggressive suppression of atrial tachyarrhythmias by pharmacology, electrical cardioversion, catheter ablation, or AVJ ablation. Frequent premature ventricular beats also must be treated (drug therapy or ablation of the PVC foci) to ensure 100% of ventricular pacing.[59]

Remote Monitoring

Remote monitoring of CRT devices with regular transmissions of data such as atrial/ventricular arrhythmia burden, percentage of biventricular pacing, or heart rate histograms favors a faster detection and solution of problems that could worsen the response to CRT. In the IN-TIME[60] randomized trial, the automatic, daily, implant-based, multiparameter telemonitoring significantly improved clinical outcomes (all-cause mortality, hospitalization, change in NYHA class, and symptoms) for patients with HF.

Multidisciplinary Approach and Follow-Up

Patients who receive CRT often require care from cardiology subspecialties (electrophysiology, HF specialist, imaging). Unfortunately, the care delivered is often fragmented, with limited communication between the different subspecialties. A multidisciplinary approach to CRT patients, based on consensus among electrophysiology, cardiac imaging, and HF specialists, improves the benefits of the therapy.

Mullens and colleagues[39] identified the main causes of nonresponse in a series of 75 patients treated with CRT: suboptimal medical treatment, incorrect LV lead position or device programming, and presence of uncontrolled arrhythmias (AF or frequent premature ventricular beats). A multidisciplinary approach in these nonresponders led to significant improvements in LV function and reduction of adverse events.

Altman and colleagues[61] demonstrated that integrated multidisciplinary care improved outcomes in patients receiving CRT. There was a 38% relative risk reduction of death, heart transplant, or hospital admissions over 2 years in patients who received a multidisciplinary care approach versus standard clinical care.

SUMMARY

Nonresponse to CRT therapy is still a major issue in therapy expansion. It is due to many factors, some of them modifiable. A better understanding about the importance of appropriate patient selection, LV lead placement, and device programming, together with a multidisciplinary approach and an optimal follow-up of the patients, may reduce the percentage of nonresponders.

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