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]

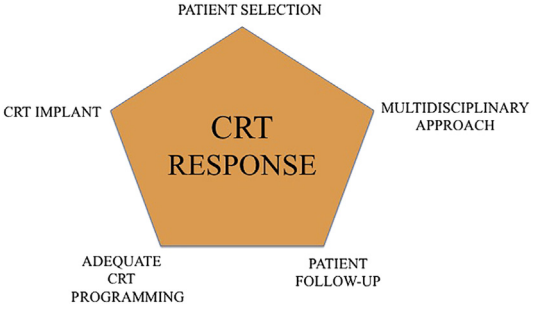

Fig. 1. Factors that could affect the response to CRT.

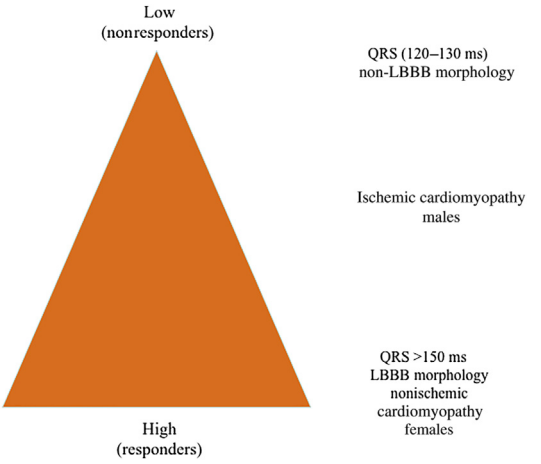

Fig. 2. Clinical factors and probability of response to CRT. (*Adapted from* Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (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]