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EDITORIAL COMMENT

# Universal response to cardiac resynchronization therapy: A challenge still to be overcome☆

## Resposta universal à terapêutica de ressincronização cardíaca – um desafio por resolver

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Cardiac resynchronization therapy (CRT) has become established in recent years as a cornerstone in the treatment of chronic heart failure (HF) in selected patients with moderate to severe left ventricular (LV) dysfunction and intraventricular conduction disturbances refractory to optimal medical therapy.

Following the pioneering work of Cazeau and coworkers in 1994,[1] a series of clinical trials[2–8] including over 4000 patients validated this strategy, which in 2005 was considered a class I indication, level of evidence A.[9] Many more trials on CRT followed, and it is now recognized as one of the most important treatment options for HF.[10,11]

Despite its acknowledged efficacy, multicenter randomized trials have reported that 20-40% of patients (depending on the criteria used) do not respond to CRT.[12]

Precise determination of the response rate to CRT is hampered by the lack of uniformity in definitions of a CRT responder.

The effects of CRT are seen at various levels. Acute hemodynamic improvement is seen very early, in the first few days after implantation of the biventricular device, reflected in symptomatic relief (reduced fatigue, more comfortable sensation of heartbeat, and better tolerance of lying down), clinical benefit (improved quality of life, functional capacity and exercise tolerance), and structural recovery. The latter is the best measure of response to CRT, and is manifested by decreased ventricular volume, increased LV ejection fraction, and reduced functional mitral regurgitation.

This favorable anatomical and functional evolution, termed reverse remodeling,[13,14] is associated with a significant reduction in clinical events such as episodes of HF decompensation, hospitalizations and cardiovascular mortality, including sudden death.

Even so, the efficacy of the different stages of CRT depends on many factors, a major one of which is patient selection.

Chronic HF may have different etiologies, which can influence the quality of response to CRT. Another variable is the mechanical dysfunction underlying cardiac dyssynchrony, and the resulting functional repercussions can vary between patients even when the electrocardiographic patterns of intraventricular conduction disturbance are similar.

It is thus clear that successful CRT requires the presence of mechanical dyssynchrony (as reflected by corresponding electrical manifestations), the definition of which has defied all efforts to standardize, even with the addition of echocardiographic exams to the candidate selection process.[15] Other factors that can affect the success of the therapy are the degree of myocardial viability, the extent of scarring and fibrosis, and anatomical variations in the veins of

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the coronary sinus, but these factors are often not assessed before device implantation. In addition, success rates are influenced by the experience of the center, optimization of medical therapy and device programming (both of which should be adjusted according to the patient's clinical and structural evolution), and the availability of appropriate cardiac rehabilitation programs, since these can promote an earlier and better response.

When instituted early in the course of the disease, the clinical benefits of CRT may not be obvious – since the patient's functional capacity is still largely preserved – but it does have a preventive function, slowing the natural history of HF as expressed by progressive structural alterations and dysfunction (cardiac remodeling) associated with increased risk of fatal cardiac events such as pulmonary edema and malignant ventricular arrhythmias, which in turn hamper reverse remodeling. Halting exacerbation of symptoms by preventing disease progression is itself a sign of a positive response, given our knowledge of the natural history of HF.

Accordingly, patients in less symptomatic stages of HF (New York Heart Association [NYHA] classes I and II) are now recommended for referral for CRT, which was originally only intended for those in NYHA classes III and IV. This recommendation, which is designed to increase the benefit of CRT and prevent patients from progressing to the advanced stages of HF, is based on evidence from three large reference studies: the REVERSE (REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction) trial,[16] which showed evidence of significant reverse remodeling in NYHA classes I and II; MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy),[17] which reported a reduction in heart failure events; and RAFT (the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial),[18] in which mortality was significantly lower in the CRT group.

In my opinion, and as also shown in some studies,[19,20] another important factor may be the site of LV pacing when there is functional mitral regurgitation, a common situation that is associated with worse prognosis.[21] Stimulation of the most proximal segment of the posterolateral wall improves coaptation of the mitral valve leaflets, leading to earlier depolarization and hence contraction of the posterior papillary muscle, which is delayed by conduction disturbances within the left ventricle. CRT reduces functional mitral regurgitation, which together with reverse remodeling (reduction in chamber and mitral annulus size), results in better response to CRT.

The efficacy of CRT has been improved by technical advances, particularly the development of smaller leads that enable better positioning, thereby increasing procedural success. The advent of quadripolar leads has the potential to increase response rate by offering different pacing options[22] and, with some devices, providing multipoint pacing.[23] These new leads also avoid problems associated with diaphragmatic stimulation, which can cause therapy to be suspended or require surgical revision with its attendant risks.[24] The different ventricular pacing options include pacing at more than one site in the right or left ventricle using a three-lead device; this technique appears to be associated with increased cardiac output and shortened QRS.[25]

Another technological advance is remote monitoring, which improves safety by enabling earlier detection and solution of problems in the pacing system; reports on various parameters that enable the patient's clinical course to be monitored, particularly in terms of HF decompensation; and records the percentage of effective biventricular pacing, permitting optimization of resynchronization and hence improving response to CRT. It has been demonstrated that when pacing exceeds 97%, there is a significant fall in overall and HF mortality and an increase in reverse remodeling.[26] Remote monitoring is especially useful in patients with atrial fibrillation or frequent premature ventricular contractions.[27]

Various studies and meta-analyses have set out to identify factors that can help or hinder a positive response to CRT. It is now known that non-ischemic cardiomyopathy,[28] female gender,[29] and left bundle branch block, especially with QRS >150 ms and sinus rhythm, are the characteristics most likely to result in a positive CRT response. The type of LV lead and its position, device programming, and operator experience are also important. CRT is definitely recommended in cases of atrial fibrillation,[30,31] if treated by atrioventricular node ablation or effective pharmacological heart rate control that can ensure nearly 100% biventricular pacing. By contrast, the presence of ischemic cardiomyopathy, particularly when there is extensive scarring[32] in the target area for pacing (the posterolateral wall) or of comorbidities such as chronic kidney disease or significant valve disease, have been shown to reduce response rates, while right bundle branch block[33] and narrow QRS (<120 ms)[34] should be considered exclusion criteria for CTR.

Another important factor in candidate assessment is right ventricular (RV) dysfunction, the role of which in selection for CRT has recently been the subject of considerable research and debate, with different studies showing conflicting results. The main cause of RV dysfunction, which is often an indication of advanced disease, is chronic LV dysfunction. RV dysfunction is also a strong independent predictor of mortality in patients with chronic HF secondary to LV dysfunction.[35,36]

Some authors consider that the presence of RV dysfunction is not an impediment to referral for CRT,[37] an attitude that is supported by the results of studies that show significant gains in RV size and function following CRT[38,39] and even recovery of RV function following resynchronization therapy.[40]

In contrast to these positive findings, other authors have argued that impaired RV function in itself significantly limits the ability of CRT to bring about reverse LV remodeling and is a strong prognostic factor identifying patients who have already undergone extensive cardiac remodeling and who will therefore not benefit from CRT.[41–44]

The above background highlights the importance of the article by Abreu et al.[45] published in this issue of the *Journal*, on a prospective cohort study that addresses the question of CRT response and helps clarify the role of RV function. The authors found that of the different baseline characteristics that can influence response to CRT, only preserved RV function as reflected by tricuspid annular plane systolic excursion (TAPSE) >15 mm was an independent predictor of echocardiographic response, defined in this study as improvement in LV ejection fraction of 5% or more. They

also showed that patients with TAPSE <15 mm at initial assessment did not respond to CRT, which may help to identify patients who should not be referred for this therapy.

The study emphasizes once again the importance of referral for CRT at an early stage of the disease, in order to prevent progression to RV dysfunction, which will compromise the degree of response.

It is likely that in the near future patients will be selected for CRT on the basis of scores that use a range of variables, and some such tools have already been proposed.[46,47]

In conclusion, research should continue into the characteristics that determine CRT response, in order to ensure appropriate selection of candidates who will benefit from this therapy and to identify factors that hamper response, in order not to expose those unsuitable for CRT to unnecessary risks and to avoid wastage of resources.

## Conflicts of interest

The author has no conflicts of interest to declare.

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