What We Can Learn from "Super-responders"

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KEYWORDS

• CRT • Left ventricular ejection fraction • Cardiac resynchronization therapy
• Left ventricular function

KEY POINTS

- In patients treated with cardiac resynchronization therapy (CRT) presenting an important improvement of left ventricular (LV) function, the long-term outcome is excellent.
- Super-responders have a low absolute risk of severe ventricular tachyarrhythmias; however, some cardiac events can occur several years after implantation despite normal or near-normal LV function.
- In patients with CRT with a defibrillator undergoing device replacement, a downgrading to CRT with a pacemaker should be considered with caution.

INTRODUCTION

Cardiac resynchronization therapy (CRT) has largely demonstrated to improve heart failure (HF) symptoms, left ventricular (LV) function and even survival in about 70% of patients with symptomatic HF, reduced LV ejection fraction (LVEF) and intraventricular conduction delays especially in patients with left bundle branch block (LBBB), regardless of HF etiology.[1,2] On this basis, current international guidelines suggest, as class IA recommendations, CRT implantation in patients with symptomatic HF (New York Heart Association [NYHA] class III and IV), QRS duration greater than 120 milliseconds, and severe reduction of LVEF ($\leq$35%). Even less symptomatic patients (NYHA class II) may benefit from CRT in terms of long-term survival in the presence of longer QRS duration ($\geq$150 ms).[3,4] In some patients ("super-responders"), we observe an exceptional clinical and instrumental improvement after CRT with the patient becoming almost asymptomatic (NYHA class I) with a normalization or near-normalization of the LVEF (>50%). In addition to an improvement of quality of life, super-response to CRT leads to a decrease in the incidence of hospitalizations for HF symptoms, a decrease of the incidence of implantable cardioverter defibrillator (ICD) appropriate therapies, and eventually to a survival gain.[5]

The intended outcome for almost every patient undergoing CRT to become a "super-responder." Response to CRT depends on several factors, such as patient characteristics (ie, etiology, comorbidities) and anatomic features of the cardiac venous system and procedural aspects (ie, preprocedural planning, device selection), but the characteristics of super-responders to CRT are less well-studied than those of nonresponders and negative responders.

This review discusses the state of the art of knowledge in this field to help decision making in patients candidates to CRT and to analyze the long-term total and cardiac mortality, sudden death, and CRT with a defibrillator (CRT-D) intervention rate, as well as the evolution of echocardiographic parameters in patients with LVEF of greater than 50% after CRT implantation. Owing to "NYHA normalization" of LV function in super-responders, the need for a persistent defibrillator backup is also considered.

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DEFINITION OF SUPER-RESPONDERS TO CARDIAC RESYNCHRONIZATION THERAPY

Thus far, there is no full agreement concerning the definition of super-responders to CRT. Several clinical, instrumental, and combined criteria have been suggested.[6] Instrumental response to CRT is usually assessed by echocardiography quantifying reverse LV remodeling by changes in LV end systolic volume and/or LVEF at 3 to 6 months after CRT implantation. In these terms, an absolute normalization of LVEF (≥50%) or improvement by almost 30% has been suggested as criteria for super-response.[5,7] Some studies suggests that LV reverse remodeling, more than the improvement in LVEF, is the best predictor of outcome.[8,9]

From a clinical point of view, response to CRT can be evaluated by improvement in NYHA functional class to II or I or better as quantified by the 6-minute walk test.[10,11] Probably the best definition of super-response to CRT is a combination of both clinical measures and imaging parameters[12]; thus, a clinical (NYHA class I or II) and echocardiographic (ie, LVEF ≥50%) definition of super-response should be encouraged as a standard definition.[13] However, an inconsistency exists between clinical and echocardiographic response in favor of the clinical response; less than 50% of patients who experience clinical improvement show significant LV reverse remodeling.[11,14] In the large trial Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT),[15] an absolute increase of LVEF of almost 18% was able to identify patients with better prognosis at follow-up, and for this reason it has been suggested as the more reliable parameter to evaluate response to CRT. In particular, a recent subanalysis of the MADIT-CRT population[16] demonstrated an improvement in LVEF from 29.5 ± 3.2% at baseline to 40.5 ± 5.9% at 12 months ($P<.001$). Of 752 patients, 55 (7.3%) achieved an LVEF of greater than 50%, whereas 594 patients (79%) achieved an LVEF of 36% to 50%, and the remaining 103 (13.7%) maintained a 35% or lower LVEF.

FROM BENCH TO BEDSIDE: CARDIAC RESYNCHRONIZATION THERAPY AND REVERSE REMODELING

The so-called ventricular remodeling is the pathophysiologic process that leads to a modification of LV geometry, dimensions, and structure after any type of myocardial injury. In the early stage of myocardial structural disease, LV remodeling represents a compensatory modification to maintain an adequate LVEF and systemic output thanks to the Frank–Starling rule. Unfortunately, as the remodeling continues, it sets up a vicious cycle leading to a progressive loss of contractility.

Ongoing HF is accompanied by a progressive dilation and loss of ellipsoidal shape by the LV in favor of a spherical one. The spherical shape increases wall stress as well as oxygen consumption. Moreover, it leads to a displacement of papillary muscles, leading to an incomplete cooptation of mitral leaflets that increases the severity of mitral regurgitation, which in turn increases the LV end diastolic filling pressure and depresses the ejection fraction, perpetuating further the vicious cycle.

This general principle makes it easy to understand how important action against ventricular remodeling can be. CRT shapes reverse remodeling, leading to a decrease in LV diameters and volume from the first months after implantation.[17] Within the first 6 to 12 months after implantation, there is a progressive LV reverse remodeling with a decrease in end diastolic and end systolic LV volumes, an improvement of LVEF with a decrease in the sphericity index, and a decrease in the severity of mitral regurgitation.[18,19] Reverse remodeling is observed regardless of the etiology of the dysfunction, although it tends to be more significant in patient affected by nonischemic cardiomyopathy.

Mechanisms of reverse remodeling are not fully understood, but probably involve wall stress and oxygen consumption reduction, lowering of sympathetic tone, and improvement of mitral regurgitation. CRT induces changes in the gene expression pattern of genes involved in contractile function and pathologic hypertrophy and modifies levels of HF biomarkers.[20] In super-responders, there is a decrease in absolute myocardial fibrosis, the apoptotic index, and of tumor necrosis factor-α levels.[21]

PREVALENCE AND PREDICTORS OF SUPER-RESPONSE TO CARDIAC RESYNCHRONIZATION THERAPY: LONG-TERM PROGNOSIS

Super-response to CRT has been reported to range between 7.3% and 40%.[14,16,22–24] Super-responders to CRT have shown not only a better quality of life owing to an amelioration of HF symptoms, but also a significant improvement in overall survival, a reduction in ICD appropriate therapy, and a decrease in hospitalizations for HF.[15] Mortality reduction goes along improvement of LVEF and reduction of LV volumes, confirming that the beneficial effect of CRT is largely attributable to reverse remodeling.[25]

Several studies have investigated predictors of super-response to CRT. Results show a

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