Case presentation: A 55-year-old female patient underwent implantation of a cardiac resynchronization therapy (CRT) defibrillator 6 years ago owing to nonischemic dilated cardiomyopathy. Her left-ventricular (LV) ejection fraction (EF) was 28% before implantation, her LV end-diastolic volume index (EDVI) was 144 mL/m², and her LV end-systolic volume index (ESVI) was 104 mL/m². Her intrinsic QRS complex was 155 ms with left bundle-branch block morphology. Despite being on optimal medication, she still experienced symptomatic heart failure (New York Heart Association class III). Now, 6 years later, she is doing very well (New York Heart Association class II). Her LVEF has increased to 38%, her EDVI has decreased to 95 mL/m², and her ESVI has decreased to 59 mL/m². Is this patient a superresponder to CRT? Were any of her baseline characteristics predictive for superresponse? What are the implications regarding her prognosis and clinical management?

The Scope of the Problem

CRT is a cornerstone in contemporary heart failure management because of the reduction in morbidity and mortality after CRT implantation in patients who have the triad of: (1) symptomatic chronic heart failure (CHF), (2) a severely reduced LVEF (EF \( \leq 35\% \)), and (3) a wide QRS complex. The benefit to the individual patient, however, may vary widely. Although some demonstrate a good or even excellent response to CRT (referred to as superresponders), others show little to no effect. Indeed, evidence is accumulating that CRT may even induce harm in some individuals, especially in patients with a narrow QRS complex.

The Definition of Superresponse to CRT and Its Impact on Prognosis

What is the definition of nonresponse to CRT? Given the natural course of patients with CHF, stabilization of the disease indicates some response, whereas true nonresponders continue their downward course, and negative responders may even derive harm from CRT (Figure 1). The characteristics of superresponders to CRT are less well studied than those of nonresponders. There is no consensus regarding the definition of superresponse. Indeed, several different echocardiographic parameters characterize superresponders in different settings, including an improvement in ESVI, EDVI, and EF (Table). The cutoff values are not consistent among different studies, even if the parameter used to define superresponse is the same. Finally, some studies rely at least in part on clinical variables to define superresponse.

Superresponse to CRT appears to be associated with a favorable prognosis. Lower long-term mortality and fewer CHF hospitalizations are observed in patients demonstrating a decrease in ESVI \( \geq 30\% \) after CRT. In a recent subanalysis of The Multicenter Automatic Defibrillator Implantation Trial – Cardiac Resynchronization Therapy (MADIT-CRT), patients in the highest quartile of EF improvement after 1 year (mean absolute LVEF improvement, +17.5%) had a combined rate of CHF hospitalization and all-cause mortality of 4% in comparison with responders (11%) and hyporesponders (lowest quartile of EF improvement, 26%).

To facilitate interstudy comparability and practices, we compared different definitions of superresponse to CRT. We found that all 3 definitions of superresponse—an absolute increase in LVEF \( \geq 10\% \), a decrease in ESVI \( \geq 30\% \), or a decrease in EDVI \( \geq 20\% \)—are associated with a favorable outcome after CRT. As such, despite the absence of a formal consensus on the actual definition of superresponse, currently used parameters and cutoffs seem to be reliable in depicting patients with a favorable clinical outcome.
The time point after CRT implantation to evaluate patients is important. Too early an assessment may underestimate the degree of reverse remodeling. Most studies (Table) chose a period between 2 and 12 months after implantation for follow-up echocardiography. Indeed, after 1 year of CRT, little to no further reverse remodeling may be expected in the majority of patients (eg, patients with extensive intraventricular conduction disease (ie, wide QRS complexes) and left bundle-branch block block are more likely to become superresponders to CRT.4,5 Similarly in the MADIT-CRT trial, QRS duration of ≥150 ms and left bundle-branch block in addition to female sex, lack of prior myocardial infarction (and hence, most likely, lack of significant scar area), body mass index <30 kg/m², and smaller baseline left atrial volume index are predictive of LVEF superresponse.7 This is consistent with the repeated observations that patients with left bundle-branch block and prolonged QRS complex (>150 ms) generally respond better to CRT (Figure 2).3,10

Accordingly, the most recently updated ESC guidelines for CRT grade their recommendations according to QRS duration and the presence or absence of left bundle-branch block.1

A relatively short duration of heart failure symptoms before CRT implantation is associated with CRT superresponse,2,6 indicating that earlier implantation after the establishment of the diagnosis of severe CHF results in a higher chance of pronounced reverse remodeling. Indeed, these observations are consistent with the general paradigm of a point of no return in the natural course of CHF.11,12 Available data hence do not support withholding CRT for eligible patients on optimal medical therapy, and indicate a benefit of proceeding to CRT implantation without delay.

Turning Nonresponders into Superresponders
Optimizing device programming is important.13 Appropriately adjusting these settings, however, requires extensive experience in the programming of these devices.

Optimization of the mode of ventricular stimulation may lead to an increase in the proportion of CRT responders. One algorithm, called adaptive CRT, provides only LV pacing synchronized to produce fusion with the intrinsic activation of the right ventricle.14 Patients randomly assigned to the adaptive algorithm had a better clinical outcome (less death or CHF hospitalization) than those with standard biventricular pacing and echocardiographic optimization. This is contradictory in part to the results of the GREATER-EARTH trial, in which LV stimulation was not superior to standard biventricular pacing by stimulation from 2 different LV sites, as opposed to one (termed multisite pacing). Preliminary studies demonstrated greater hemodynamic benefit by using this method over standard biventricular pacing and an increased propensity for echocardiographic

Table. Parameters and Cutoffs Used to Define Superresponse to CRT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cutoff</th>
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<tbody>
<tr>
<td>EF²</td>
<td>≥50% and Functional recovery</td>
</tr>
<tr>
<td>EF⁶</td>
<td>&gt;2× baseline or &gt;45% or NYHA ≥1 class</td>
</tr>
<tr>
<td>ESV⁴</td>
<td>− ≥30%</td>
</tr>
<tr>
<td>EF¹⁹</td>
<td>≥50% and ESV ≥25% and Improvement in NYHA class</td>
</tr>
<tr>
<td>EF⁵</td>
<td>+ ≥20%</td>
</tr>
<tr>
<td>ESVI *</td>
<td>− ≥30%</td>
</tr>
<tr>
<td>EDVI *</td>
<td>− ≥20%</td>
</tr>
<tr>
<td>EF² *</td>
<td>+ ≥10%</td>
</tr>
<tr>
<td>EF³</td>
<td>Top quartile of EF change</td>
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</tbody>
</table>

MADIT-CRT LIFR, presented at the 2013 congress of the European Society of Cardiology). However, in the Cardiac Resynchronization in Heart Failure Study (CARE-HF) and other randomized, controlled trials, the reduction in morbidity and mortality becomes apparent only after 12 months, suggesting that other factors may be involved in the beneficial effect of CRT.

Predictors of Superresponse
Because superresponse is highly predictive of a good clinical outcome, pre-implantation characteristics predictive of superresponse are of prime interest. Patients with extensive intraventricular conduction disease (ie, wide QRS complexes) and left bundle-branch block more likely become superresponders to CRT.4,5

Figure 1. Possible clinical courses after CRT implantation. Responders show a measurable effect, whereas superresponders show excellent response up to normalization after CRT implantation. Nonprogressors do not show a benefit of CRT, but also do not follow their predicted natural course of deterioration as a result of CHF (dashed line) like nonresponders. Negative responders demonstrate clinical worsening of their disease after CRT implantation. CHF indicates chronic heart failure; and CRT, cardiac resynchronization therapy.
response (presented at the 2013 meeting of the Heart Rhythm Society). Whether these algorithms will transform nonresponders to responders or even to superresponders will require further study; however, they are promising options in patients without an adequate response to standard biventricular pacing.

**CRT Superresponse as a Predictor of Future Arrhythmic Events?**

Because superresponse to CRT is associated with a favorable clinical outcome, it is tempting to speculate that severe arrhythmic events (ventricular tachycardia and fibrillation) will be less frequent in this patient population. This issue may arise when superresponders are due for a device change and the implantation of a smaller (and cheaper) CRT pacer instead of a CRT-defibrillator is contemplated. Indeed, it may be argued that patients demonstrating extensive reverse remodeling as a result of superresponse to CRT would per se no longer meet current implantable cardioverter defibrillator indications. However, primary prevention implantable cardioverter defibrillator trials have not been performed in CRT superresponders. The few studies that have investigated this issue found a lower rate of ventricular arrhythmias in patients with pronounced LV reverse remodeling. In the MADIT-CRT trial, ventricular tachyarrhythmias were clearly lowest in superresponders (as defined by a reduction in ESV ≥ 25%). Despite the pronounced reduction in ventricular tachyarrhythmias, however, ventricular tachycardias were also observed in these patients (12% tachyarrhythmias and 5% with first appropriate shock over 2 years in MADIT-CRT superresponders). Similarly, in a recent retrospective study, even superresponders experienced appropriate implantable cardioverter defibrillator discharges.

CRT provides epicardial LV stimulation, which may cause ventricular arrhythmias in CRT patients because of an increase in transmural dispersion of repolarization. Indeed, nonsuperresponders in MADIT-CRT had a similar or even higher rate of ventricular arrhythmias than implantable cardioverter defibrillator recipients (ie, patients without biventricular stimulation). Hence, 2 competing effects of CRT may be operative: on the one hand, a reduction in the probability of ventricular tachyarrhythmias attributable to reverse remodeling, but on the other hand, a proarrhythmic effect, particularly (albeit not exclusively) in those patients with less pronounced LV reverse remodeling. Taken together, these data indicate that all patients, even superresponders, are prone to experience ventricular arrhythmias. As a result, exchange of the CRT-defibrillator for a CRT-pacemaker at the time of generator replacement cannot generally be recommended, even for superresponders.

**Are Superresponders Dependent on Continued Biventricular Stimulation?**

Especially in view of a potentially proarrhythmic effect of CRT (as discussed above), it may be tempting to cease biventricular stimulation once a pronounced effect on (or even normalization of) LV size and function has occurred. This rationale, essentially, leads to the question of whether superresponse represents genuine cure or only excellent control of the disease. Comprehensive data are currently lacking to answer this question. Although sustained clinical and echocardiographic response may rarely be observed even after the deactivation of biventricular pacing, confounders including spontaneous clinical remission (eg, as a result of a correctable cause such as acute myocarditis or tachycardiomyopathy) need to be considered. Indeed, small-scale studies of superresponders in CHF have mainly demonstrated a progressive decrease in LV function following the cessation of biventricular stimulation, suggesting that CRT may control but not cure the disease.

Deactivation of LV stimulation may become an option in certain clinical scenarios, including refractory diaphragmatic stimulation (as a result of altered LV geometry attributable to extensive remodeling) or arrhythmias presumed to be attributable to epicardial LV stimulation. In these cases, careful and close monitoring of clinical status and LV function is indispensable. If clinical deterioration ensues, LV lead repositioning should CRT reactivation be considered.
Conclusion

Although desirable, a universal definition of superresponse to CRT does not exist. Independent of the definition, however, superresponders with pronounced LV reverse remodeling do demonstrate a superior clinical outcome. Despite the impressive reduction in terms of morbidity and mortality in these patients, close specialized follow-up to review their clinical state and their device programming needs to be implemented to maximize their outcome.

Case Disposition

In view of her impressive increase in LVEF with concomitant reduction in ESVI and EDVI, our patient is a superresponder. Indeed, she carried several positive predictors for superresponse, including a wide QRS complex, left bundle-branch block, female sex, and nonischemic cardiomyopathy. As a result, she clearly has a favorable prognosis regarding morbidity and mortality. In view of currently available data, however, generator replacement should encompass the reinplantation of a CRT-defibrillator device, because she remains at risk for ventricular arrhythmias despite her substantial reverse remodeling.

Disclosures

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Superresponse to Cardiac Resynchronization Therapy
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