Clinical Trials

Predictors and Outcomes of "Super-response" to Cardiac Resynchronization Therapy

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ABSTRACT

Background: Cardiac resynchronization therapy (CRT) has been shown to improve heart failure (HF) symptoms and survival. We hypothesized that a greater improvement in left-ventricular ejection fraction (LVEF) after CRT is associated with greater survival benefit.

Methods and Results: In 693 patients across 2 international centers, the improvement in LVEF after CRT was determined. Patients were grouped as non-/modest-, moderate-, or super-responders to CRT, defined as an absolute change in LVEF of ≤5%, 6−15%, and >15%, respectively. Changes in New York Heart Association (NYHA) functional class and left ventricular end-diastolic dimension (LVEDD) were assessed for each group. There were 395 non-/modest-, 186 moderate-, and 112 super-responders. Super-responders were more likely to be female and to have nonischemic cardiomyopathy, lower creatinine, and lower pulmonary artery systolic pressure than non-/modest- and moderate-responders. Super-responders were also more likely to have lower LVEF than non-/modest-responders. There was no difference in NYHA functional class, mitral regurgitation grade, or tricuspid regurgitation grade between groups. Improvement in NYHA functional class (-0.9 ± 0.9 vs -0.4 ± 0.8 [$P < .001$] and -0.6 ± 0.8 [$P = .02$]) and LVEDD (-8.7 ± 9.9 mm vs -0.5 ± 5.0 and -2.4 ± 5.8 mm [$P < .001$ for both]) was greatest in super-responders. Kaplan-Meier survival analysis revealed that super-responders achieved better survival compared with non-/modest- ($P < .001$) and moderate-responders ($P = .049$).

Conclusions: Improvement in HF symptoms and survival after CRT is proportionate to the degree of improvement in LV systolic function. Super-response is more likely in women, those with nonischemic substrate, and those with lower pulmonary artery systolic pressure. (*J Cardiac Fail 2014;20:379−386*)

Key Words: Cardiac resynchronization, ICD, pacemaker, heart failure, treatment.

In recent years, cardiac resynchronization therapy (CRT) has become an integral tool in the management of heart failure (HF), with landmark trials showing both morbidity and mortality benefit in those with impaired left ventricular ejection fraction (LVEF), prolonged QRS duration, and New York Heart Association (NYHA) functional class III−IV symptoms despite optimal medical therapy.[1−4] In 2012, guidelines were revised to expand the indication to patients with NYHA functional class II symptoms if they have left bundle branch block (LBBB) and/or QRS duration ≥150 ms, based on recently published MADIT-CRT, RAFT, and REVERSE trials.[5−7] However, the high

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variability of benefit derived among responders has attracted attention, with some improving so much as to regain near-normal cardiac function and anatomy.[8] Such ''super-responders'' seem to derive survival benefit, and several studies have tried to address predictors of both response[9−11] and super-response.[12−15] This, however, is somewhat complicated by the absence of a universal definition of ''response.''[16−18] The expected relative and absolute increase in LVEF after CRT varies from study to study,[3,19,20] but the incidence of super-response has been shown to be 10%−20%.[8,16,21,22] In addition, the delay in response varies from 6 months to >3 years. We aimed to determine: 1) the proportion of CRT recipients who are super-responders; 2) whether a greater improvement in left ventricular (LV) function after CRT is associated with greater survival benefit; and 3) baseline characteristics that may be predictive of super-response.

Methods

Patient Population

This was a 2-center (Mayo Clinic, Rochester, Minnesota, USA; and Sheba Medical Center, Tel Hashomer, Israel) retrospective study that included 693 patients who received CRT with a defibrillator (CRT-D; n = 603) or without a defibrillator (CRT-P; n = 90) from 2002 to 2011. Clinical information documented as part of routine clinical care, such as NYHA functional class, cause of HF, and other demographic characteristics, were collected from electronic medical records. The Institutional Review Board of each center approved the protocol, and all patients consenting to use of their records for research were included in the study.

Echocardiography

Registered diagnostic cardiac sonographers from each center performed echocardiography, and echocardiographer cardiologists interpreted results. Echocardiography parameters recorded included LVEF (calculated using the modified Simpson's formula), LV end-diastolic dimension (LVEDD; measured with m-mode or 2-dimensional echocardiography), LV end-systolic dimension (LVESD), LV end-diastolic volume (LVEDV; calculated with the Teichholz formula), LV end-systolic volume (LVESV; calculated with the Teichholz formula), pulmonary artery systolic pressure (PASP; estimated from the tricuspid regurgitant [TR] velocity and an estimate of right atrial pressures), mitral valve regurgitation (MR) grade (0, none; 1, trivial/mild; 2, moderate; 3, severe; based on jet characteristics and/or proximal isovelocity surface area method), and right ventricular (RV) dysfunction (semiquantitative grading scale: 0, normal; 0.5, borderline; 1, mild; 1.5, mild-moderate; 2, moderate; 2.5, moderate-severe; 3, severe dysfunction). Intraventricular dyssynchrony was not routinely measured during the study period. Preimplant echocardiographic data were collected within 12 months before the CRT implant and postimplant echocardiographic data were collected within 15 months after the CRT implant.

Cardiac Resynchronization Therapy

Device implantation was performed under conscious sedation and local anesthetic as standard clinical practice.[23] The position of the LV lead was prioritized as lateral/posterolateral, anterolateral, anterior, and middle cardiac veins whenever possible as dictated by pacing thresholds, diaphragmatic stimulation, and ability to cannulate the veins. Standard settings (which could be individualized according to the implanting physician) were programmed. Patients were hospitalized and continuously monitored overnight. Repeat device interrogation was performed on the following day. Device pocket was examined, and chest x-ray was obtained. Patients were dismissed when discharge criteria were met.

Clinical Follow-up

After implantation, patients were asked to return for follow-up per standard procedure. All 693 patients had quantification of LVEF with repeated echocardiography and reassessment of HF symptoms. The mean (±SD) time from CRT implantation to post-CRT echocardiography was 8.5 ± 3.8 months. The device was interrogated to ensure normal function. Survival information was obtained from the electronic medical records and the national death and location database (Accurint, Lexisnexis for Mayo Clinic patients) for 465 patients from Mayo Clinic (data obtained November 2011) and 228 patients from Sheba Medical center (data obtained July 2012). No routine atrioventricular and ventriculoventricular optimization was performed.

Definition of Response

Patients were classified as non-/modest-responders, moderate-responders, and super-responders based on the absolute change in LVEF from before to after CRT, via echocardiography assessment, of ≤5%, 6%−15%, and >15%, respectively.

Statistical Analysis

We tested for baseline differences in characteristics among the 3 LVEF responder groups (non/modest, moderate, and super) with the use of Kruskal-Wallis tests for continuous measures and chi-square tests for categoric measures. When overall tests were significant ($P < .05$), we also tested for pairwise differences in super-responders compared with non-/modest- and moderate-responders with the use of Wilcoxon rank sum test or chi-square tests. Changes in measures from before to after CRT were assessed with the use of Wilcoxon signed rank tests within groups. Changes in measures were compared between groups with the use of linear regression adjusting for time from CRT implantation to post-CRT echocardiography. We summarized survival with a Kaplan-Meier curve for each group. Log-rank tests were used to assess differences in survival across the 3 responder groups and pairwise differences in survival among the groups. Survival time was defined as time from follow-up echocardiography to date of death or last follow-up. Univariable Cox proportional hazard models were fitted to assess baseline predictors of survival. Measures that were significant at $P < .05$ in the univariable models were included in a final multivariable model along with time from CRT implantation to post-CRT echocardiography, as well as baseline measures that were significantly different among the response groups. The assumption of proportional hazards for each variable in the multivariable model was assessed by examining the correlations between each variable and the Schoenfeld residuals. Logistic regression was used to assess baseline predictors of super-response in univariable models and a multivariable model defined in a manner similar to the above.