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ORIGINAL ARTICLE

Who Are the Super-Responders to Cardiac Resynchronization Therapy?

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Abstract

Background: Patients submitted to cardiac resynchronization may develop response patterns that are higher than expected, with normalization of clinical and echocardiographic parameters.

Objective: To analyze the clinical and echocardiographic characteristics of this population of super-responders, comparing them with the other patients submitted to cardiac resynchronization therapy.

Methods: A prospective, observational cohort study involving 146 patients consecutively submitted to cardiac resynchronization implants. Fisher's exact test and Mann-Whitney test were performed to compare the variables. Patients with ejection fraction > 50% and functional class I/II (New York Heart Association) were considered super-responders after 6 months of cardiac resynchronization therapy.

Results: Mean age was 64.8 ± 11.1 years, with 69.8% of males, with a median ejection fraction of 29%, 71.5% with left bundle-branch block, 12% with right bundle-branch block associated with hemiblocks; 16.3% wearing a definitive cardiac pacemaker, 29.3% with ischemic cardiomyopathy, 59.4% with dilated cardiomyopathy, and 11.2% with Chagasic cardiomyopathy. Twenty-four (16.4%) super-responders were observed, and 13 (8.9%) showed normalization of the ejection fraction, left ventricular diastolic diameters and functional class. When compared to the non-super-responder patients, in relation to the pre-implantation characteristics, the super-responders were more often females (58.3% vs. 22.8%, p = 0.002), had higher body mass index (26.8 vs. 25.5, p = 0.013), higher baseline ejection fraction (31.0 vs. 26.9, p = 0.0003), and lower left ventricular diastolic diameters (65.9 mm vs. 72.6 mm, p = 0.0032). Ten patients (41.6% of super-responders) with right bundle-branch block and hemiblock progressed to super-responders, although there was only one patient with Chagas' disease among them, and only at the first assessment.

Conclusions: Super-responders had less advanced heart disease at baseline and no differences regarding the type of conduction disorder at baseline. Patients with right bundle-branch block and hemiblock, but without Chagasic heart disease may also progress as super-responders. (Int J Cardiovasc Sci. 2017;30(1):61-69)

Keywords: Heart Failure; Cardiac Resynchronization Therapy; Echocardiography; Defibrillators, Implantable.

Introduction

Cardiac Resynchronization Therapy (CRT) has shown good results in the treatment of Congestive Heart Failure (CHF) in patients with conduction disorders, marked left ventricular dysfunction and outpatient New York Heart Association (NYHA) functional classes (FC) II, III and IV, being included as class I and higher level of scientific evidence in the several guidelines for cardiac device implants and CHF.[1]

However, 30 to 40% of the patients may not have a good outcome after CRT, thus being called non-responders. The classification of responders and non-responders is very heterogeneous in the several performed studies.[2] The fact is, the criteria for the definition of an adequate CRT response is still in question

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and it is not possible to define response predictors with precision and consensus.[2,3]

Some authors have described groups of patients that progressed with higher responses than the expected ones, with normalization of left ventricular function, FC, and ventricular diameters, thus being called hyper-responders or Super-Responders (SR), ranging from 9 to 21% in several studies.[4-6] The characteristics of these patients have been assessed, and the super-response is interpreted as a possible cardiomyopathy induced by cardiac dyssynchrony, caused by the intra-ventricular conduction disorder.[7] Predictors of super-response are the female gender, non-ischemic heart disease (Chagas cardiomyopathy not included) and Left Bundle-Branch Block (LBBB).[8]

This study aimed to analyze the clinical and echocardiographic characteristics of a cohort of patients submitted to cardiac resynchronization implants that progressed as SR, comparing them with other patients implanted in the same period.

Methods

This was a prospective, observational, and single-center study of a cohort of 146 consecutive patients submitted to cardiac resynchronization implants at a tertiary university hospital during a 3-year period. Only patients who failed to successfully receive an electrode implant in the coronary sinus were excluded from the analysis. Implant indications comprised patients with Ejection Fraction (EF) ≤ 35%, outpatient FC III or IV (NYHA), intraventricular conduction disorder with QRS width ≥ 120 ms and optimized CHF treatment.

Patients were divided into two groups after clinical and echocardiographic analysis in the first year. Group I comprised SR and Group II, Non-Super-Responders (NSR). Patients who died before the protocol was finished were considered as Group II. Patients who did not maintain the pattern defined as SR during the second year of assessment were kept in Group I and their characteristics were analyzed. There was no loss to follow-up in either group. Patients in FC I or II and EF ≥ 50% after 6 months of implantation were considered SR.[5]

The patients were submitted to clinical and echocardiographic assessment in the first year (6 to 12 months after the implantation) and in the second year (18 to 24 months after), as well as clinical consultations every 4 months for therapeutic optimization and programming of the implanted devices. The characteristics of patients included in the study are shown in Table 1.

Table 1 – Description of baseline variables

Baseline variables	Results
Male gender	69.8%
Female gender	30.2%
Age	64.8 ± 11.1
FC III	68.1%
FC IV	31.9%
Use of beta-blocker	88.7%
Use of ACEI	97.4%
Use of high-dose diuretics	31.9%
BMI	25.8 ± 4.1
Cardiac cachexia	6.36%
Number of previous hospitalizations	108
At least 1 hospitalization	64.3%
Chagasic heart disease	11.2%
Ischemic heart disease	29.3%
Dilated heart disease	59.4%
Right QRS axis deviation	1.8%
Left QRS axis deviation	87.0%
Normal axis	10.1%
Previous QRS width	160 ms
Post-implant QRS width	140 ms
QRS delta	28.6 ± 24.8
Atrial fibrillation	12%
LBBB	71.55%
RBBB with hemiblocks	12%
Pacemaker rhythm	16.3%
Pacemaker carrier	28.3%
Ejection fraction	29%
DD, grade	
IV	11.8%
III	29.7%
II	23.7%
I	34.6%
MVR mild	50.4%
IM moderate	30.4%
IM severe	15.6%
RV dysfunction	20.9%
LVDD	70 mm
Systolic BP	115 ± 17 mmHg
Diastolic BP	70 mmHg
Posterolateral vein	45.4%
Anterolateral vein	52.5%
Dyssynchronization*	80. 4%
Creatinine	1.1 mg/dL
ICD	54.2%

*The pre- and post-implant QRS widths, the R wave size at V1 shunt in patients with LBBB, the ejection fraction and LVDD were expressed as medians (non-normal variables). Age and BMI are shown as means with standard deviation. *Dyssynchronization was analyzed in 46 patients. FC: functional class; ACEI: angiotensin-converting enzyme inhibitors; BMI: body mass index; LBBB: left bundle branch block; RBBB: right bundle branch block; DD: diastolic dysfunction; MVG: mitral valve regurgitation; RV: right ventricle; LVDD: left ventricular diastolic diameter; BP: blood pressure; ICD: implantable cardioverter-defibrillator.*

Analyzed variables

The following clinical, electrocardiographic and echocardiographic variables were analyzed: clinical variables – age, gender, Body Mass Index (BMI), presence of cardiac cachexia, NYHA-FC, baseline heart disease, cardiac vein in which the LV electrode was placed, plasma creatinine levels, systolic blood pressure, diastolic blood pressure, use of high dose-loop diuretics (≥ 80 mg/day of furosemide), hospitalizations from CHF; Electrocardiographic variables – presence of atrial fibrillation, type of block, cardiac pacing, presence of first-degree atrioventricular block (AVB), QRS duration, QRS narrowing after implantation (QRS delta), QRS axis in the frontal plane, before and after implantation; Echocardiographic variables: LV diastolic and systolic diameters, EF measured by the Simpson method, diastolic dysfunction degree from I to IV, degree of mitral regurgitation from I to III, presence of right ventricular dysfunction, presence and type of cardiac dyssynchrony.

The American Society of Echocardiography guidelines were followed for the analysis of echocardiographic and dyssynchrony parameters.[9,10] Recommendations for clinical studies involving echocardiography were strictly followed, in accordance with this specific North-American guideline.[10] The GE, Vivid 7® model (GE Healthcare, Fairfield, CT, USA) echocardiography equipment was used. The physicians performing the examinations were blinded for the patients' previous clinical and echocardiographic findings, and had experience in evaluating patients, such as those included in the study.

The variables selected to constitute the models represented relevant, practical and conventional parameters in the electrocardiographic and echocardiographic evaluation of patients with cardiomyopathy – several already showing a positive association with clinical and / or prognostic improvement.[11]

The systolic function analysis was performed using the Simpson method, in two- and four-chamber two-dimensional mode, followed by the mean. Ventricular diameters were obtained in M mode according to the standardization of the guidelines.[10] Right ventricular function was qualitatively analyzed, differentiated between the presence or absence of any degree of dysfunction.

The diastolic function analysis was performed by assessing mitral flow (at rest and after the Valsalva maneuver), tissue Doppler, and the flow propagation velocity in the M mode with color, being classified into four different diastolic dysfunction degrees (I for Mild, II for moderate or pseudonormal, III for severe or restrictive, and IV for severe or irreversible restrictive pattern).

The degree of mitral regurgitation was assessed using color Doppler, according to the percentage of left atrial filling. In mild regurgitation, the percentage was less than 20%; in the moderate, between 20% and 40%, and values above this percentage were considered important. In this practical context, the Coanda effect was interpreted as moderate reflux, when restricted to the lateral atrial wall and, as marked, when it extended through the upper pole of the left atrium.

Statistical Analysis

The Shapiro-Wilks normality test was performed to classify the normal variables. The variables creatinine, diastolic blood pressure, R wave length, QRS width, EF and left ventricular diastolic diameter (LVDD) were not normally distributed.

The behavior of the variables of interest was compared through the Mann-Whitney test for ordinal, discrete and continuous variables, and Fisher's exact test and its extensions for the categorical variables, with a significance level of 5% to determine the statistically different behaviors in the two groups. The data were analyzed using Stata / SE, version 12.1 (StataCorp LP, College Station, TX, USA) and R software (R Foundation for Statistical Computing, Vienna, Austria).

The study was approved by the Ethics and Clinical Research Committee of the university hospital, and all patients signed the free and informed consent form. The study protocol followed the ethical standards of the Helsinki Declaration.

Results

There were 30 deaths during the follow-up of 34.0 ± 17.9 months, which represents 23.1% of overall mortality. Analyzing all patients together, 88.6% improved at least one degree in FC (NYHA); 51.7% reduced the number of hospitalizations from CHF; 50% improved more than 5% in absolute EF values and 87% decreased more than 5 mm in the LVDD. Of the 46 patients evaluated for the presence of dyssynchrony, 37 (80.4%) had some degree of previous dyssynchrony; 35 (76%) intraventricular, 16 (34.7%) interventricular, 15 (32.6%) atrioventricular and 9 (19.5%) had no dyssynchrony.

There were twenty-four (16.3%) SR (Group I) and 13 (8.8%) patients had EF, LV diastolic diameters and FC normalization. Compared with the NSR patients (Group II) in relation to baseline, pre-implantation characteristics, Group I patients had more women (58.3% vs. 22.8%, $p = 0.002$), higher BMI (26.8 vs. ($p < 0.05$), higher baseline EF (31.0% vs. 26.9%, $p = 0.0003$) and lower LVDD (65.9 mm x 72.6 mm, $p = 0.0032$) (Tables 2 and 3).

The SR had a higher incidence of pre-implantation dyssynchronization at the 10% level of significance ($p = 0.072$) and a lower percentage of patients using high-dose loop diuretics ($p = 0.087$). Regarding the type of cardiopathy, no differences were observed when comparing the three types simultaneously (dilated cardiomyopathy – DCM, Chagasic cardiomyopathy and ischemic cardiomyopathy). When DCM vs. other cardiomyopathies were analyzed together, the SR showed a higher incidence of DCM ($p = 0.035$).

Ten patients (41.6% of total SR) with Right Bundle-Branch Block (RBBB) and Hemiblock (HB) became SR, with no difference in relation to patients with self-LBBB or LBBB induced by stimulation. When we analyze LBBB vs. RBBB/HB and induced LBBB, the SR showed a lower incidence of LBBB alone ($p = 0.043$).

In the group of patients with Chagas cardiomyopathy (11.2%) submitted to CRT, only 15.3% had RBBB /HB; 30.7% had artificial stimulation rhythm and 54% had LBBB. Only one patient with Chagas' disease evolved as SR and it occurred temporarily, limited to the first evaluation.

One patient from the SR group lost control of the coronary sinus electrode in the third year after implantation, showing clinical worsening and hemodynamic deterioration. After implantation of a new epicardial electrode, a new normalization of left ventricular function and diastolic diameters occurred at 4 months.

Of the 15 patients with complete clinical and echocardiographic normalization, only two were observed late (in the second year of evaluation), whereas of the other nine SR patients, it occurred late in five, but without complete normalization of all parameters and in two, it occurred transiently and limited to the first year of evaluation.

Regarding the diastolic function, two patients developed grade II diastolic dysfunction and the others, grade I. All SR progressed to grade I of mitral regurgitation. No patient with complete normalization of EF, LVDD and FC migrated to Group II during follow-up.

Three patients in SR group died: one due to breast cancer, the other due to respiratory infection and another was transplanted due to persistent ventricular arrhythmia and died postoperatively.

Table 2 – Comparison of numerical variables between Group I, Super-Responders (SR), and Group II, Non-Super-Responders (NSR), pre-implantation

Variable	Group I	Group II	p value
BMI (kg/m²)	26.8 ± 4.6	25.5 ± 3.9	0.013*
Age (years)	65.2 ± 7.6	64.7 ± 11.9	0.994
QRS width	162.6 ± 20.0	166.2 ± 23.8	0.644
Post-implant QRS width	124.3 ± 13.7	129.7 ± 22.3	0.706
Delta QRS	38.1 ± 17.0	26.2 ± 26.0	0.673
Ejection fraction	31.0 ± 3.5	26.9 ± 5.1	0.0003*
LVDD	65.9 ± 8.3	72.6 ± 9.8	0.0032*
Creatinine	0.97 ± 0.2	1.2 ± 0.3	0.75
Diastolic pressure	75.0 ± 9.7	70.8 ± 11.5	0.77
Systolic pressure	120.4 ± 18.9	113.7 ± 16.3	0.65

**Significant variable at the 5% level. BMI: body mass index; LVDD: left ventricular diastolic diameter.*

Table 3 – Comparison of the categorical variables in Group I, Super-Responders (SR), and Group II, Non-Super-Responders (NSR) pre-implantation

Variable	Group I (%)	Group II (%)	p value
Female gender	58.3	22.8	0.002*
Cachexia	8.3	5.8	0.645
Chagas vs. other cardiopathies	4.1 vs. 95.8	13.0 vs. 86.9	0.29
DCM vs. other cardiopathies	79.1 vs. 20.8	54.3 vs. 45.6	0.035*
LBBB/PM vs. RBBB/HB	87.5 vs. 12.5	88.0 vs. 11.9	≈ 1
LBBB vs. RBBB/HB/PM	54.1 vs. 45.8	76.0 vs. 23.9	0.043*
Grade 1 AVB	42.6	26.0	0.160
Atrial fibrillation	16.6	10.8	0.483
FC III vs. IV	62.5 vs. 37.5	69.5 vs. 30.4	0.623
RV dysfunction	22.7	20.2	0.775
Diastolic dysfunction Grade III/IV	47.3	33.3	0.293
MR Grade I/II/III	66.6 vs. 20.8 vs. 8.3	50 vs. 32.6 vs. 17.3	0.115
Dyssynchrony	90	75	0.072†
Hospitalization from CHF	62.5	64.8	0.815
AL vs. PL coronary vein	56.5 vs. 43.4	63.1 vs. 36.8	0.628
Previous pacemaker	37.5	26.0	0.312
Beta-blocker	87.5	89.1	0.730
ACEI	95.8	97.8	0.504
≥ 80 mg furosemide	16.6	35.8	0.087†

**Significant variable at 5% level; † significant variable at the 10% level. DCM: dilated cardiomyopathy; LBBB: left bundle branch block; PM: pacemaker; RBBB: right bundle branch block; HB: hemiblock; AVB: atrioventricular block; FC: functional class; RV: right ventricle; MR: mitral regurgitation; CHF: congestive heart failure; AL: anterolateral; PL: posterolateral; ACEI: angiotensin-converting enzyme inhibitors.*

Discussion

The SR were predominantly female patients, with a likely better nutritional status, higher EF and lower LVDD. Patients receiving lower amounts of high-dose loop diuretics (≥ 80 mg furosemide a day), and with a higher degree of pre-implant dyssynchrony showed a trend towards statistically significant results when compared to NSR.

Less advanced heart disease has shown better results with CRT, disclosing good results in recent studies with patients in FC II, and unsatisfactory results in subanalyses of patients with FC IV, particularly when hospitalized or dependent on vasoactive drugs. The results of this study corroborate that of others who also demonstrated hyper-responsive patterns in patients with less advanced heart disease.[5,6,12]

In the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) study, in patients with mild symptoms of heart failure, the female gender, absence of infarction, LBBB, QRS > 150 ms, BMI < 30 kg/m^2 and reduced left atrial volume were predictors of SR.[8] Our study included a group of patients with very symptomatic CHF, with 64% of patients having been previously hospitalized for recently decompensated CHF. These differences in the population characteristics may explain some differences in the observed results.

Patients with RBBB + HB showed super-response with no difference in relation to LBBB or patients with LBBB induced by cardiac stimulation. When we analyzed the conventional LBBB in relation to the other electrocardiographic patterns (right branch and LBBB induced by the PM), we observed a lower chance of SR with conventional LBBB. These results show differences in comparison to the literature, which demonstrates a clear advantage of classic RBBB in the CRT results. However, in relation to hyper-responsiveness or super-response, the studies do not attain a consensus in their conclusions. We believe that the patients in our study with RBBB, because they had associated HB and a wider QRS (median of 160 ms), should have a significant degree of dyssynchrony, which could justify the absence of differences. Another reason may be due to the lower number of patients analyzed in our study, determining a statistical limitation.

However, in a study of 200 patients with CHF, Haghjoo et al.[13] evaluated 110 patients with RBBB with or without Left Anterior-Superior Hemiblock (LASHB) and 90 patients with LBBB. Mechanical dyssynchrony was investigated through tissue Doppler echocardiography. Patients with isolated RBBB had a lower prevalence (33%) of interventricular dyssynchrony (defined as a delay of more than 40 ms in the aortic and pulmonary pre-ejection intervals) than patients with LBBB (54%) or RBBB plus LASHB (50%), with statistical significance. As for the intraventricular dyssynchrony (defined by standard deviation of 12-segment pre-ejection intervals greater than 34 ms), it was more prevalent in patients with LBBB (58%) than in those with RBBB (28%) or RBBB with LASHB (42%), with $p < 0.001$. The presence of intraventricular dyssynchrony, in this case considered an important predictor of resynchronization response, could not be correlated to the presence of HB: patients with RBBB, with or without LASHB, did not show statistical difference.[13]

To date, most of the information that has accumulated regarding the role of CRT in the treatment of CHF comes from studies that evaluated patients predominantly with LBBB. Patients with RBBB were less representative in clinical trials (less than 15%) and, therefore, little can be definitively inferred regarding the efficacy of resynchronization in this scenario.[14,15] Our study shows that RBBB patients when associated with HB can also become as hyper-responders, especially in the absence of Chagasic heart disease.

Even though the changes induced by dyssynchrony are proposed as an essential condition for the resynchronization response, the effect of this therapy can be mediated by other pathways, such as the previous degree of diastolic dysfunction and ventricular dilatation.[16] The multicenter study, PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) was unable to correlate the different types of dyssynchronization, evaluated by 12 echocardiographic parameters, with the response to CRT, having as justifications the variabilities in the techniques used and the method interpretations.[17] However, in the SR subgroup, the PROSPECT study showed a higher incidence of previous dyssynchrony, in addition to a larger group of women, non-ischemic heart disease and wider QRS.[18]

LV reverse remodeling has been used as a standard to define response in most new studies.[2,19,20] Patients with LV end-systolic volume shortening > 10%, in analyses of 3 to 6 months, would be considered responders; greater than 15%, hyper-responders; and below 10%, non-responders, with a sensitivity of 70% and specificity of 70% in predicting total mortality. For cardiac mortality, the sensitivity was 87% and the specificity was 69%. Other studies used the LV end-systolic volume > 30% to define the SR and, more classically, the EF normalization[12] associated with the reduction in FC.[5]

When DCM was compared to other heart diseases, a greater chance of hyper-responsiveness was observed in the DCM, as described in the literature. The degree of fibrosis observed in patients with ischemic and Chagasic cardiomyopathy could explain these findings. However, these patients were not previously submitted to cardiac viability assessment or nuclear magnetic resonance imaging to confirm such hypothesis. Chagasic heart disease has been associated with a lower response rate in CRT, probably related to the higher severity of this cardiopathy and higher incidence of RBBB.[21] In our study, 15.3% of the patients with Chagas disease had RBBB, and only one became a SR and then, only transiently.

The reasons for better responses among the female patients in the group submitted to CRT and better results among males submitted to ICD implants have raised discussions in the literature, without definitive conclusions. We also observed a higher BMI in the SR group, which could reflect better nutritional status and, consequently, less advanced heart disease, but the numerical differences are clinically difficult to evaluate and may reflect small variations in volume retention.

The use of high doses of loop diuretics has been shown to be a marker of severity in cardiomyopathy, including in the group of patients submitted to CRT, when analyzed before implantation, as well as 1 year after the CRT.[22] The presence of a higher incidence in the NSR group may reflect this aspect.

Regarding the cardiac function normalization time, most SR showed these results in the first year, with a small portion showing slight worsening in parameters in the second year. Therefore, the SR pattern occurs more frequently in the first 12 months after CRT, a finding also observed in other studies.[23]

The possibility of cardiac function normalization in 15 to 20% of patients submitted to CRT has been an intriguing and encouraging finding, considering they are severe patients, with poor prognosis in the medium and long term.[7] Cay et al.[24] demonstrated cardiomyopathy recurrence and ventricular function worsening in the SR group when multisite stimulation was switched off. Thus, it is necessary to analyze the group of hyper- or SR in greater depth. They may represent an important target in CRT, constituting the possibility of cure in a subgroup of patients.

Limitations

This was a single-center study, which involved a not very large population of 147 patients submitted to CRT and analyzed 24 (16.3%) SR. No intra- or inter-observer analysis was performed on electrocardiographic and echocardiographic variables. The dyssynchrony analysis was performed in only 46 patients, without the possibility of statistical analysis of subgroups. No adjustments were made for the AV interval by the echocardiogram after the implant. Feasibility and fibrosis assessments were not performed by magnetic resonance imaging prior to implantation. New echocardiographic techniques, such as strain, were not evaluated. Patients with isolated RBBB were not included in the analysis. The study did not have statistical power of mortality analysis between the studied groups.

Conclusions

The super-responders represented 16.4% of the patients submitted to cardiac resynchronization therapy, 8.9% with functional class, left ventricular diastolic diameter and ejection fraction normalization. These patients had less advanced heart disease at baseline and no differences regarding the type of baseline conduction disorder.

Patients with right bundle-branch block associated with left hemiblocks may also develop a super-response. Chagasic heart disease was less likely to be overresponsive, even in the presence of left bundle-branch block.

Author contributions

Conception and design of the research: Rocha EA, Pereira FTM, Abreu JS, Lima JWO, Rodrigues Sobrinho CRM, Scanavacca MI. Acquisition of data: Rocha EA, Pereira FTM. Analysis and interpretation of the data: Rocha EA, Pereira FTM, Quidute ARP, Abreu JS, Lima JWO, Scanavacca MI. Statistical analysis: Rocha EA, Quidute ARP, Abreu JS, Lima JWO. Obtaining financing: Rocha EA. Writing of the manuscript: Rocha EA, Quidute ARP, Rodrigues Sobrinho CRM, Scanavacca MI.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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