



Original Article

Incidence and predictors of super-response to cardiac resynchronization therapy

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ABSTRACT

Objectives: Cardiac resynchronization therapy (CRT) has significantly improved management of patients with heart failure with reduced ejection fraction (HFrEF). A significant number of patients have a dramatic response and have been termed “super-responders”. The characteristics of this subset of patients in Indian and Asian population have not been well studied. In this study, we sought to assess the prevalence and clinical characteristics of this cohort of patients.

Methods: This was a retrospective study involving patients undergoing CRT. Changes in ejection fraction and LVESV at the end of one year of follow-up following device implantation were assessed, and patients were stratified into non-responders, responders, and super-responders. Responders had a 15–29% decrease in LVESV while super-responders had a >30% decrease in LVESV.

Results: Of the 74 patients who had undergone CRT-P/CRT-D implantation, 16 patients did not have echocardiograms at the end of one year of follow-up and were excluded from the analysis. Thus, 58 patients were enrolled for analysis. We identified 16 patients (27.6%) to be super-responders, 26 patients (44.8%) to be responders, and 16 patients (27.6%) to be non-responders. Factors associated with a super-response were a diagnosis of dilated cardiomyopathy as against ischemic cardiomyopathy (93.7% vs 6.3%; $p = 0.01$), prior right ventricular (RV) apical pacing (25% vs 2.4%; $p = 0.02$) and absence of a prior history of myocardial infarction (MI) (0% vs 33.3%; $p = 0.02$).

Conclusion: In our study, 27.6% of patients were super-responders, and a diagnosis of dilated cardiomyopathy, absence of a prior history of MI and prior RV apical pacing predicted a super-response to CRT.

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1. Introduction

Heart failure is an important cause of morbidity and mortality affecting more than 5 million individuals worldwide. Numerous advances, both pharmacological and non-pharmacological, have led to improved outcomes in patients with heart failure. Nearly 15–30% of patients with left ventricular (LV) systolic dysfunction have intraventricular conduction delays which leads to dyssynchronous ventricular contraction further compromising ventricular performance and systolic function.^{1,2} Cardiac resynchronization therapy which aims to synchronize ventricular activation and contraction has considerably improved both the mortality and morbidity in patients with LV systolic dysfunction.^{3,4} However, the response to cardiac resynchronization therapy in terms of improvements in LV systolic function and clinical symptoms is varied

with nearly 30% being classified as non-responders. In contrast to this is a cohort of patients termed super-responders who demonstrate a dramatic response to cardiac resynchronization therapy (CRT) with considerable improvement in symptoms and near normalization of ejection fraction. However, clinical identifiers of this cohort of patients are still unclear.

The incidence of super-responders among Indian patients and their clinical characteristics has not been well described. We sought to identify the proportion of patients with a super-response to CRT among our patients undergoing CRT and to recognize clinical characteristics which identified this cohort of patients.

2. Materials and methods

2.1. Study population

This was a retrospective study performed in the Department of Cardiology at our center, including all patients undergoing CRT

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implantation by the author from 2011 to 2016. All patients undergoing CRT and with paired echocardiograms at 1 year apart were included in the study. CRT-P/CRT-D implantation was done in patients with a LV ejection fraction less than 35%, left bundle branch block (LBBB) on the electrocardiogram (ECG) with a QRS duration greater than 130 ms and in New York Heart Association (NYHA) class II/III/IV. LBBB was defined in accordance with previously defined criteria.⁵

In patients with ischemic cardiomyopathy, LV ejection fraction and LV end systolic volumes/end diastolic volumes were measured by Simpson's method, while in patients with non-ischemic cardiomyopathy, they were measured using Simpson's method and/or Teichholz method. While the Simpson's method is the recommended echocardiographic gold standard for calculation of LV volumes, the Teichholz method was used in cases of technical difficulty in employing Simpson's method in patients with non-ischemic cardiomyopathy. Care was taken to ensure the same method was used for assessing LV volumes both at baseline and at 1 year follow-up.

The response to CRT was defined based on the reduction in LVESV at 1-year follow-up. A less than 15% decrease in LVESV was defined as a "non-response", a 15–30% decrease in LVESV was defined as a "response" while a greater than 30% decrease in LVESV was defined as a "super-response".⁶

2.2. Statistical analysis

All data were collected prospectively and entered into a spreadsheet program (Microsoft Excel 2016™, Microsoft Corporation, Redmond, WA). Statistical analysis was done using the Statistical package for social sciences (SPSS Inc. version 23.0™, IBM Corporation, Chicago, IL). All continuous variables were summarized as mean $\pm$ standard deviation. Categorical variables were described as proportions and frequencies (%). The comparison between two groups for continuous variables was done by using the Student *t*-test. The comparison between two categorical variables was done by using the chi-square test or Fisher's exact test.

3. Results

A total of 74 patients were identified who underwent CRT from 2011 to 2016. Of these, nine patients died within 1 year, and seven patients were lost to follow-up at the end of 1 year and were excluded from the analysis. A total of 58 patients were included in the final analysis (Fig. 1).

The mean age at device implantation was 62 ± 10.5 years. 51.7% ($n = 30$) of patients were males, while 48.3% ($n = 28$) were females.

Table 1

Baseline characteristics of study patients.

Clinical characteristics	CRT ($n = 58$)
Age (years)	62 ± 10.5
Sex	
Male	30 (51.7)
Female	28 (48.3)
Cardiac risk factors	
Diabetes mellitus	18 (31)
Hypertension	18 (41.4)
Smoking	8 (17.4)
Prior history of pacemaker insertion	5 (8.6)
Dilated cardiomyopathy	39 (67.2)
Ischemic cardiomyopathy	19 (32.8)
NYHA class II	16 (27.5)
NYHA class III	39 (67.2)
NYHA class IV	3 (5.3)
QRS duration >140 msec	43 (74.1)
LV – RV msec	86.8 ± 17.1
Ejection fraction (%)	26.3 ± 7
Left ventricular (LV) volume	
LVEDV (ml)	184.7 ± 52.3
LVESV (ml)	136.6 ± 55.3
Secondary Mitral regurgitation	
None	3 (5.2)
Mild	35 (60.3)
Moderate	13 (22.4)
Severe	7 (12.1)

Msec, milliseconds; ml, milliliter; CRT, cardiac resynchronization therapy; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume. Categorical variables expressed as N (%).

Continuous variables expressed as mean $\pm$ standard deviation.

Dilated (non-ischemic) cardiomyopathy was the most common etiology accounting for 39 patients (67.2%), while ischemic cardiomyopathy was the etiology in 19 patients (32.8%). Of the 39 patients with non-ischemic cardiomyopathy, five patients had pacing induced cardiomyopathy from a previously implanted dual chamber pacemaker.

While a QRS duration greater than 130 ms was used as inclusion criteria for CRT, 74.1% ($n = 43$) of patients had a QRS duration greater than 140 ms and fulfilled the Strauss criteria for LBBB.⁷

The mean LV ejection fraction at baseline was $26.3\% \pm 7\%$, while the mean LVESV and LVEDV were 136.6 ± 55.3 mL (ml) and 184.7 ± 52.3 mL, respectively.

The electrophysiologic separation of the LV lead from the right ventricular (RV) lead was assessed by measuring the LV – RV interval on intracardiac electrograms. The mean LV – RV interval was 86.8 ± 17.1 ms (Table 1).

Sixteen patients had a less than 15% reduction in LVESV and were classified as "non-responders", 26 patients had a 15–30%

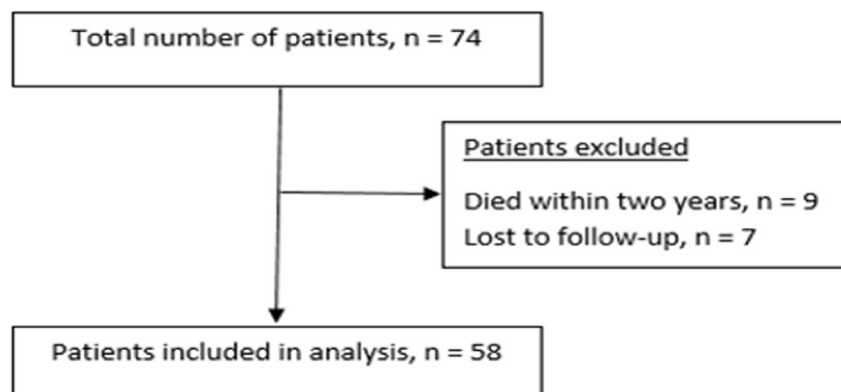


Fig. 1. Study population.

Table 2

Characteristics of non-responders, responders, and super-responders.

Clinical characteristics	Non-responders (n = 16)	Responders (n = 26)	Super-Responders (n = 16)
Age (years)	59.8 ± 11.3	62.6 ± 10.1	62.2 ± 11
Sex			
Male	11 (68.8)	13 (50)	6 (37.5)
Female	5 (31.3)	13 (50)	10 (62.5)
Diabetes mellitus	6 (37.5)	7 (26.9)	5 (31.3)
Hypertension	3 (18.8)	14 (53.8)	7 (43.8)
Dilated cardiomyopathy	8 (50)	16 (61.5)	15 (93.8)
Ischemic cardiomyopathy	8 (50)	10 (38.5)	1 (6.2)
LV – RV (msec)	91.5 ± 19.3	83.4 ± 18	86.9 ± 17.2
Percentage change in LVESV (ml)	15 ± 17.4	23.8 ± 13	67.1 ± 31.4
Ejection fraction (%)			
Pre	24.1 ± 3.6	27.5 ± 4.7	28.4 ± 5.2
Post	27.1 ± 4.8	36.5 ± 6	50.1 ± 7.5
Change	3 ± 2.6	9 ± 3	21.7 ± 6.7
Change in NYHA class	12 (75)	26 (100)	16 (100)
HF-related hospitalization	4	2	2
Change in mitral regurgitation			
No change	4 (25)	7 (26.9)	1 (6.3)
Change by 1 grade	11 (68.8)	15 (57.7)	12 (75)
Change by 2 grades	1 (6.3)	3 (11.5)	3 (18.8)
Change by 3 grades	0	1 (3.9)	0

Msec, milliseconds; ml, milliliter; HF, heart failure.

Categorical variables expressed as N (%).

Continuous variables expressed as mean ± standard deviation.

reduction in LVESV and were classified as “responders”, while 16 patients had a greater than 30% reduction in LVESV and were classified as “super-responders” (Tables 2 and 3).

A higher proportion of super-responders were females (62.5% vs 32.9%; $p = 0.18$). Fifteen of the 16 super-responders (93.7%) had non-ischemic cardiomyopathy, with four of these patients having pacing induced cardiomyopathy. Only one patient with ischemic cardiomyopathy had a super-response (1/19). Contrastingly, 18 of the 42 (42.9%) responders/non-responders had ischemic cardiomyopathy (93.7% vs 57.1%; $p = 0.01$).

A prior history of myocardial infarction was present in 14 responders/non-responders, while no super-responder had a history of myocardial infarction (33.3% vs 0%; $p = 0.01$).

Among the five patients with RV pacing induced cardiomyopathy, four had a super-response to CRT with near normalization of ejection fraction, while one patient was a responder with a 23% reduction in LVESV.

CRT may also result in significant improvements in mitral regurgitation (MR). In our patients, an improvement in MR by at least one grade was seen in 46 patients (85.6%) (Table 2).

Clinical response to CRT was evaluated in terms of improvement in NYHA class. Four patients (25%) in the non-responder group, and

all patients in the responder and super-responder groups had an improvement by at least one NYHA class. Heart failure-related hospitalization was seen in eight patients within the first year of implantation—four of these patients belonged to the non-responder group while two each were from the responder and super-responder groups.

4. Discussion

Cardiac resynchronization therapy has a varied response with a success rate of 70% with nearly 30% of patients being classified as non-responders.⁸ At the other end of the spectrum is the subgroup of patients termed super-responders who have marked improvements in LV ejection fraction and reduction in LVESV. Various studies have identified a super-responder rate ranging from 10% to 30%.^{9,10}

In our study, we found a super-responder rate of 27.6% ($n = 16$). Non-ischemic cardiomyopathy, absence of a prior history of myocardial infarction and RV pacing-induced cardiomyopathy were predictors of a super-response to CRT. Nonischemic cardiomyopathy (NICM) appears to have a more favorable response to CRT than ischemic cardiomyopathy (ICM). Gasparini et al. in a study

Table 3

Comparison of super-responders with non-super-responders.

Clinical characteristics	Super- Responders n = 16 (27.6%)	Non-super-Responders n = 42 (72.4%)	p value
Age (years)	62.2 ± 11	61.6 ± 9.6	
Sex			
Male	6 (37.5)	24 (57.1)	0.18
Female	10 (62.5)	18 (42.9)	
Diabetes mellitus	5 (31.3)	13 (31)	0.98
Hypertension	7 (43.8)	17 (40.5)	0.82
Smoking	0	6 (14.3)	0.11
Dilated Cardiomyopathy	15 (93.7)	24 (57.1)	0.01
Ischemic cardiomyopathy	1 (6.3)	18 (42.9)	
Prior RV pacing	4 (25)	1 (2.4)	0.02
Prior history of myocardial infarction	0	14 (33.3)	0.01

Msec, milliseconds; ml, milliliter; RV, right ventricular.

Categorical variables expressed as N (%).

Continuous variables expressed as mean ± standard deviation.

of 158 patients found a greater improvement in LVEF and reduction in NYHA class in patients with NICM compared with patients with ICM.¹¹ This finding was subsequently confirmed in the subanalysis of several randomized studies^{12–15} emphasizing the importance of underlying substrate in predicting the response to CRT. We report a similar finding in our study with 93.7% of patients with a super-response having NICM.

Hsu et al. in a subanalysis of the Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy (MADIT-CRT) study reported the absence of a prior history of myocardial infarction as an independent predictor of a super-response to CRT, a finding also seen in our study. This likely reflects the absence of LV scar which could imply both, a greater amount of viable myocardium and the absence of scar in the region of LV lead implantation.¹⁰ One patient with ischemic cardiomyopathy in our cohort of patients had a super-response. This likely reflects the greater contribution of LV dyssynchrony, resulting from LBBB to LV dysfunction as compared with myocardial infarction and scarring.

Permanent RV pacing is a known cause of LV dysfunction resulting from the dyssynchrony induced by pacing. This cohort of patients have been shown to have an excellent response to CRT.¹⁶ In our study, all patients with pacing induced cardiomyopathy ($n = 5$) who underwent an upgrade to biventricular pacing had a good response to CRT. Biventricular pacing by ameliorating dyssynchrony restores the efficiency of cardiac contraction mechanics thus enabling recovery of LV function.

Females had a higher proportion of super-responders than males (62.5% vs 37.5%; $p = 0.18$). Females have been reported to have higher rates of response to CRT compared with males previously.¹⁰ This has been postulated to be because of a higher prevalence of NICM and LBBB among females.^{17,18} In our study, there was no difference in the distribution of ischemic cardiomyopathy and NICM between males and females.

A discrepancy has been reported between CRT response as ascertained by clinical characteristics such as improvement in NYHA class and that determined by echocardiographic characteristics such as LVEF and LVESV. The higher response rate, when assessed using subjective parameters such as NYHA class and quality of life questionnaires, has been attributed either to improvements in MR or to a contributory placebo effect resulting from device implantation. In our study, 12 of the 16 non-responders had a change in NYHA class. All of these patients had a change in MR by at-least 1 grade which might explain the improvement in symptoms.

4.1. Limitations

Our study included only those patients who had paired echocardiograms at baseline and at 1 year follow-up. A total of nine deaths occurred in our cohort of patients before the completion of 1 year of follow-up, and these were not included in our analysis. Two of these patients had progressive heart failure, while the cause of death in the remaining seven patients could not be ascertained. The exclusion of these nine patients would constitute a bias as inclusion of these patients as non-responders would have resulted in a reduction in rates of response.

5. Conclusion

While CRT has revolutionized the management of heart failure, a sizable proportion of patients do not show an adequate response. At the other end of the spectrum is a cohort of patients who demonstrate dramatic reverse remodeling. In our study, we found a super-response in 27.6% of patients. Underlying etiology is an

important predictor with NICM having a better response than ICM. This is the first report of a super-response to CRT from the Indian subcontinent. Further studies need to be done to further characterize this response with a view to optimize patient selection for CRT.

Conflict of interest

All authors have none to declare.

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