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Identification of 'super-responders' to cardiac resynchronization therapy: the importance of symptom duration and left ventricular geometry

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Aims Some patients show such an important clinical improvement and reverse remodelling after cardiac resynchronization therapy (CRT) that anatomy and function approach normal. These patients have been called 'super-responders'. The aim of our study was to identify predictors of becoming a super-responder after CRT.

Methods and results Eighty-seven consecutive patients who underwent CRT were prospectively studied. Before CRT and 6 months after, clinical and echocardiographic evaluation was performed. Patients with a decrease in New York Heart Association functional class $\geq$1, a two-fold or more increase of left ventricular ejection fraction (LVEF) or a final LVEF $>$45%, and a decrease in LV end-systolic volume $>$15% were classified as super-responders. There were 12% super-responders. At baseline, there were no significant differences between super-responders and the other patients, except for the fact that super-responders had significantly smaller mitral regurgitation and LV end-diastolic diameter (LVEDD) and a shorter duration of heart failure symptoms. Mitral regurgitation jet area, LVEDD, and duration of heart failure symptoms were correlated with this super-response. Moreover, an evolution of symptoms for $<$12 months was an independent predictor of super-response to CRT.

Conclusion Patients in earlier phases of the cardiomyopathy, with a less altered ventricular geometry, seem to have a greater probability of becoming super-responders.

Keywords Resynchronization therapy • Super-responders • Heart failure • Echocardiography

Introduction

Cardiac resynchronization therapy (CRT) is recommended for heart failure patients who remain in symptomatic New York Heart Association (NYHA) class III or IV despite optimal medical treatment, with normal sinus rhythm, low left ventricular ejection fraction (LVEF) ($<$35%), left ventricular (LV) dilation, and QRS duration $>$120 ms.[1,2]

Cardiac resynchronization therapy improves symptoms and exercise capacity and also decreases heart failure hospitalizations and all-cause mortality when added to optimal pharmacotherapy in patients with advanced heart failure.[3] However, up to 30% of patients receiving CRT do not have a positive clinical or reverse remodelling response.[4] In contrast, some patients who underwent CRT show such an important clinical improvement and left ventricular reverse remodelling that anatomy and function approach normal.[1] These patients have been called 'super-responders' to CRT, and it is expected that they will have the best outcome after CRT.

A decrease in LV end-systolic volume (LVESV) $>$15% is clinically relevant, because this value has a high sensitivity and specificity for the prediction of long-term all-cause and cardiovascular mortalities. Furthermore, this cut-off value of LV reverse remodelling also predicts heart failure events and composite endpoints of cardiovascular hospitalization or mortality. In fact, LV remodelling seems to be the strongest predictor of long-term survival after

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CRT. Therefore, volumetric assessment by echocardiography is not only a surrogate marker of a favourable cardiac response to CRT, but also an objective measure that predicts long-term clinical outcomes.[5]

Previously, the search for optimal and easily detectable predictors of response to CRT has attracted a lot of attention; nevertheless, there are very few data concerning super-responders to CRT. Recently, Castellant *et al.*[6] have proposed to consider patients as super-responders if they concurrently fulfilled two criteria: functional recovery and LVEF ≥50%. However, in our opinion, this definition of super-responder is not satisfactory because it does not consider LV reverse remodelling (the best predictor of long-term survival after CRT), and it should be more specific regarding LVEF. We may have patients with a very low baseline LVEF, an excellent LV reverse remodelling, and up to four-fold improvement of LVEF after CRT (for example, from 10 to 40%) who would not be considered super-responders according to the definition of Castellant *et al*. Should these patients not be considered super-responders?

At present, the mechanisms by which some patients have this excellent response to CRT and others have no benefit remain to be determined.

The aim of our study was to identify predictors of being a super-responder to CRT. We also propose a new definition of super-responders to CRT.

Methods

Inclusion criteria and study protocol

This is a prospective study that involved a single centre. The study population included 87 consecutive patients with dilated cardiomyopathy (DCM) who underwent CRT since November 2005 to October 2007. The majority of patients were in NYHA functional class III or IV, despite optimal medical treatment. All patients had echocardiographic LVEF <35% and QRS duration >120 ms (with left bundle branch block configuration), or QRS duration ≤120 ms but mechanical dyssynchrony documented by echocardiography [intraventricular dyssynchrony >40 ms and interventricular dyssynchrony (IVD) >40 ms]. The protocol was approved by our institutional Research Ethics Committee. All patients gave informed consent, and the study complied with the Declaration of Helsinki. Before CRT and 6 months after, demographic, echocardiographic, and clinical parameters (including NYHA class) were assessed. At the 6 months follow-up, patients were classified as 'super-responders' to CRT if they showed a reduction of one or more NYHA functional classes, a two-fold or more increase of the LVEF from baseline or to an absolute value >45%, and a decrease in the LVESV >15%. Non-responders were defined as patients with an improvement in LVESV ≤15% or who had been re-hospitalized for the management of chronic heart failure or died during follow-up.

Pacemaker implantation

The LV pacing lead was inserted by a transvenous approach through the coronary sinus, with an over-the-wire system, into either the lateral or postero-lateral cardiac vein whenever possible. The right atrium and right ventricle were stimulated by positioning standard bipolar catheters in the right atrial appendage and right ventricular apex, respectively. The epicardial approach was used in the case of unsuccessful conventional implantation of the LV lead. When a conventional indication for an internal defibrillator existed, a combined device was implanted. Optimization of the AV delay was performed using Doppler echocardiography, interrogating transmitral flow with the sample volume at the tip of the mitral valve leaflets in order to obtain the best flow velocity profile.

Echocardiography

Standard echocardiography, including tissue Doppler imaging (TDI), was performed using an ATL IDH 5500 Philips System (Vingmed—General Electric, Horten, Norway) before and 6 months after biventricular pacing device implantation. Left ventricular dimensions were measured from M-mode echocardiography in the parasternal long-axis view, and LV stroke volume was calculated with quantitative Doppler by multiplying the LV outflow tract by the time–velocity integral of blood flow at this level.[7] The LV end-diastolic volume (LVEDV), LVESV, and LVEF were assessed by the biplane Simpson's equation in apical four-chamber and two-chamber views.[8] The sphericity index was calculated as the ratio of LVEDV and the volume of a sphere, with a diameter equal to the LV end-diastolic long axis (LA) ($SI = 6 \times LVEDV/\pi \times LA^3$).[9] Another measurement of systolic function evaluated was mitral regurgitation d*P*/d*t*. Left ventricular diastolic function was assessed with the evaluation of LV inflow diastolic velocities with pulse-wave Doppler (*E* and *A* velocities). We assessed the ratio of peak flow velocity in early diastole and peak flow velocity in late diastole during atrial contraction (*E*/*A*), the deceleration time of E-wave, isovolumic relaxation time as the interval between the end of aortic flow and the beginning of mitral inflow, and the mitral regurgitation jet area (JA)[1] as a mitral regurgitation severity parameter. The IVD was calculated as the time difference between the aortic and pulmonary pre-ejection time intervals (from QRS to the onset of flow), where aortic and pulmonary ejection flows were recorded in the five-chamber apical and parasternal views, respectively.

To assess dyssynchrony, the time delay between the onset of QRS complex on the surface electrocardiogram and the onset of the systolic velocity wave on the TDI recording were assessed in four basal LV segments (septal, lateral, anterior, and inferior). Intraventricular dyssynchrony (T_S-Intra-VD) was calculated as the difference between the longest and the shortest time delays in the four basal segments. Additionally, IVD (T_S-Intra-VD) was calculated as the difference between time to peak systolic velocity at the right ventricular free wall and the most delayed LV segment.

Statistical analysis

Statistical analyses were performed using SPSS software version 15. Results are expressed as mean ± standard deviation or median and 25th to 75th percentiles for continuous variables and as counts and percentages for categorical variables. Data were compared with paired or unpaired Student's *t* test when appropriate. Non-parametric Mann–Whitney test was used for comparison of continuous variables between super-responders and the other patients when variables were not normally distributed. Discrete variables were compared with the χ^2 test or Fisher's exact test, whichever appropriate.

Efficacy of CRT was examined by comparing baseline vs. follow-up parameters using Student's paired *t*-test for comparisons of quantitative variables and by the McNemar test for comparisons of qualitative variables.

A multivariate, logistic regression analysis was used to identify baseline variables to be predictive of a super-response to CRT.

$P < 0.05$ was considered statistically significant.

Results

Study population

In the study population, 55 patients were males (63%) and 32 females (37%). The mean age was 62 ± 11 years. Nineteen patients were in NYHA class IV (22%), 59 in class III (68%), and 9 in class II (10%). The cause of heart failure was ischaemic in 31 (36%) patients and non-ischaemic in 56 patients. The mean duration of QRS was 145 ± 32 ms, with 14 patients (17%) presenting a QRS duration <120 ms. Thirteen patients (15%) presented with chronic atrial fibrillation (AF). Severe dilation of the LV was observed in most patients [mean LV end-diastolic diameter (LVEDD) of 75 ± 10 mm, mean LV end-systolic diameter (LVESD) of 63 ± 10 mm, mean LVEDV of 279 ± 116 mL, and mean LVESV of 214 ± 100 mL], associated with a mean LV ejection fraction of 24 ± 7%. Tissue Doppler imaging demonstrated substantial LV dyssynchrony in this population (83 ± 50 ms).

A combined device was implanted in 74% of patients (90% of the super-responders group vs. 71% of the other group, $P = 0.274$).

There were no significant differences regarding the pacemaker implantation procedure, namely in the lead position, between super-responders and the other patients.

Incidence of super-responders

Among the 87 patients with DCM, 10 (12%) demonstrated a reduction of one or more NYHA functional class, an increase in the LVEF to two-fold or more the baseline LVEF or to an absolute value >45%, and a decrease in the LVESV >15%, 6 months after CRT. These patients, who had no re-hospitalizations for the management of congestive heart failure, were considered super-responders to CRT. In 34 patients (38.4%), the LVESV did not reduce or had a reduction <15% after CRT (non-responders).

Differences of baseline characteristics between super-responders and the other patients

Regarding baseline characteristics, there were no statistically significant differences between super-responders and the other patients, except for the fact that super-responders had significantly smaller mitral regurgitation, smaller LV diastolic diameters (LVDDs), and shorter duration of heart failure symptoms (*Table 1*). Super-responders also tended to present more intraventricular dyssynchrony and IVD, higher QRS duration before CRT, and less frequently ischaemic cardiomyopathy than the other patients. However, there were no significant statistically differences between the two groups regarding these parameters.

One of the super-responders was in AF, another one had a QRS <120 ms, and two of them were in NYHA class II before CRT.

Effects of cardiac resynchronization therapy: 6 months of follow-up

After CRT, we observed a significant improvement of NYHA functional class, LVEF, LV diameters, mitral regurgitation JA, intraventricular dyssynchrony, and IVD in both groups. Left ventricular end-systolic volume showed a significant decrease in both groups; however, LVEDV reduced significantly only in the super-responder group (*Table 2*). Regarding the magnitude of response, LV volumes, LVEF, and LVESD showed a significantly greater improvement in super-responders than in the other patients (*Figure 1*). The variation of NYHA functional class, intraventricular dyssynchrony and IVD, and mitral regurgitation JA was not significantly different between the two groups.

There were no re-admissions for heart failure 6 months after CRT in the super-responder group and a re-admission rate of

Table 1 Comparison of baseline characteristics of super-responders and the other patients

	Super-responders (n = 10)	Other patients (n = 77)	P-value
Male gender (%)	60	64	0.54
ICM (%)	50	34	0.32
Age (years)	60 ± 8	62 ± 11	0.41
NYHA class	3.0 ± 0.7	3.1 ± 0.6	0.66
Duration of symptoms (months)	15.1 ± 17.8	33.9 ± 35.7	0.01
QRS duration (ms)	153.5 ± 30.8	143.5 ± 31.6	0.30
JA (cm^2)	5.4 ± 6.7	8.1 ± 5.4	0.04
LVEDD (mm)	69.3 ± 6.4	75.3 ± 10.0	0.04
LVESD (mm)	57.3 ± 7.5	63.6 ± 10.2	0.06
LVEDV (mL)	244.4 ± 72.8	267.9 ± 110.4	0.60
LVESV (mL)	192.8 ± 72.3	204.8 ± 94.0	0.79
Sphericity index	0.62 ± 0.11	0.66 ± 0.16	0.48
LVEF (%)	22.5 ± 8.6	24.4 ± 6.5	0.43
LV dP/dt (mmHg/s)	515.8 ± 247.4	476.3 ± 160.5	0.89
Intraventricular dyssynchrony (ms)	113.0 ± 96.7	78.8 ± 40.2	0.37
Interventricular dyssynchrony (ms)	57.0 ± 35.6	49.1 ± 23.4	0.35

ICM, ischaemic cardiomyopathy; JA, mitral regurgitation jet area; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction.

Table 2 Six-month follow-up results in super-responders and the other patients

6 month follow-up results	Super-responders (n = 10)	Other patients (n = 77)
NYHA class		
Baseline	3.0 ± 0.6	2.9 ± 0.6
Follow-up	1.7 ± 0.5*	2.0 ± 0.8*
LVEF (%)		
Baseline	24.5 ± 8.6	24.4 ± 6.4
Follow-up	44.2 ± 9.2*	29.6 ± 8.1*
LVEDD (mm)		
Baseline	69.3 ± 6.4	75.2 ± 10.0
Follow-up	64.5 ± 8.7*	72.7 ± 10.9*
LVESD (mm)		
Baseline	57.3 ± 7.5	63.4 ± 10.2
Follow-up	46.4 ± 9.1*	59.7 ± 11.3*
LVEDV (mL)		
Baseline	244.4 ± 72.8	267.1 ± 110.9
Follow-up	195.6 ± 65.5*	258.0 ± 124.5
LVESV (mL)		
Baseline	192.8 ± 72.3	203.8 ± 94.2
Follow-up	112.6 ± 49.8*	186.1 ± 103.2*
JA (cm^2)		
Baseline	5.9 ± 6.8	8.1 ± 5.4
Follow-up	2.7 ± 4.2*	6.2 ± 4.9*
Intraventricular dyssynchrony (ms)		
Baseline	113.0 ± 96.7	78.8 ± 40.2
Follow-up	43.0 ± 40.2*	54.2 ± 40.0*
Interventricular dyssynchrony (ms)		
Baseline	57.0 ± 35.6	49.6 ± 23.1
Follow-up	23.5 ± 30.6*	28.2 ± 27.1*

*$P < 0.05$ follow-up vs. baseline value.

10.9% in the remaining patients. No cardiac deaths occurred during the 6-month follow-up. In eight patients, there were implantable cardioverter defibrillator (ICD) shocks, which were appropriate in two cases. In super-responder group, only one patient had an ICD shock and it was inappropriate. Finally, one patient (who was not a super-responder to CRT) needed cardiac transplantation during the follow-up period.

Predictors of super-response to cardiac resynchronization therapy

In the bivariate analysis, variables correlated with super-response to CRT were mitral regurgitation JA ($r = -0.212$, $P = 0.048$), LVEDD ($r = -0.213$, $P = 0.048$), and the duration of heart failure symptoms ($r = -0.308$, $P = 0.011$). Moreover, LVEDD was inversely correlated with the improvement of LVEF after CRT (*Figure 2*).

In the multivariate logistic regression analysis, mitral regurgitation JA and LVEDD were not independent predictors of super-response to CRT. In fact, the only independent predictor of this successful result was duration of symptoms for <12 months (OR 6.03; IC: 1.17–31.02) (*Figure 3*).

Patients in New York Heart Association class II at baseline

We compared the effects of CRT in patients in NYHA class II with those in NYHA class III or IV. Before CRT, there were no significant clinical, electrocardiographic, or echocardiographic differences between the two groups, except for IVD that was higher in class II patients (117.2 ± 91.7 vs. 78.7 ± 42.4 ms; $P < 0.05$).

After CRT, NYHA class II patients showed a significant improvement of LVEF, LVESV, LVEDV, and mitral regurgitation JA. Patients in class III or IV at baseline also showed significant improvement of LVEF, LVESV, and mitral regurgitation JA, but not LVEDV (*Table 3*).

Regarding the magnitude of improvement, patients in NYHA class II presented a similar increase in LVEF and the same reduction of the mitral regurgitation as patients in NYHA class III or IV. Moreover, class II patients showed a significantly greater reduction of LV volumes (reduction of LVESV: 58.9 ± 62.7 vs. 21.0 ± 43.6 mL; $P = 0.021$ and reduction of LVEDV: 51.2 ± 56.0 vs. 9.3 ± 46.5 mL; $P = 0.014$).

There were no re-hospitalizations for heart failure management during follow-up in patients in NYHA class II at baseline. However, patients in NYHA class III or IV at baseline presented re-hospitalization rate of 7.7%.

These results suggest that the benefit of CRT in class NYHA II patients is the same or even greater than that demonstrated for patients in higher functional classes.

Discussion

Despite the encouraging results from CRT in recent trials, patient responses to CRT may vary significantly. Some patients can do worse or do not improve at all after CRT and others can have a super-response to CRT.

Proportion and predictors of super-responders

In our population, 12% of the patients treated with CRT for refractory heart failure can be identified as super-responders. This proportion is similar to previously reported results, ranging from 13 to 16%.[6,10]

This ideal response was more likely to occur in patients with less altered ventricular geometry. In fact, patients with lower LV diameters and mild-to-moderate mitral regurgitation seem to have a greater probability of having a complete reverse remodelling and becoming super-responders after CRT than those with severely altered ventricular geometry. However, neither LVEDD nor mitral regurgitation JA were independent predictors of super-response to CRT. Likewise, despite the trend of super-responders to have more dilated idiopathic cardiomyopathy, to have a wider QRS,

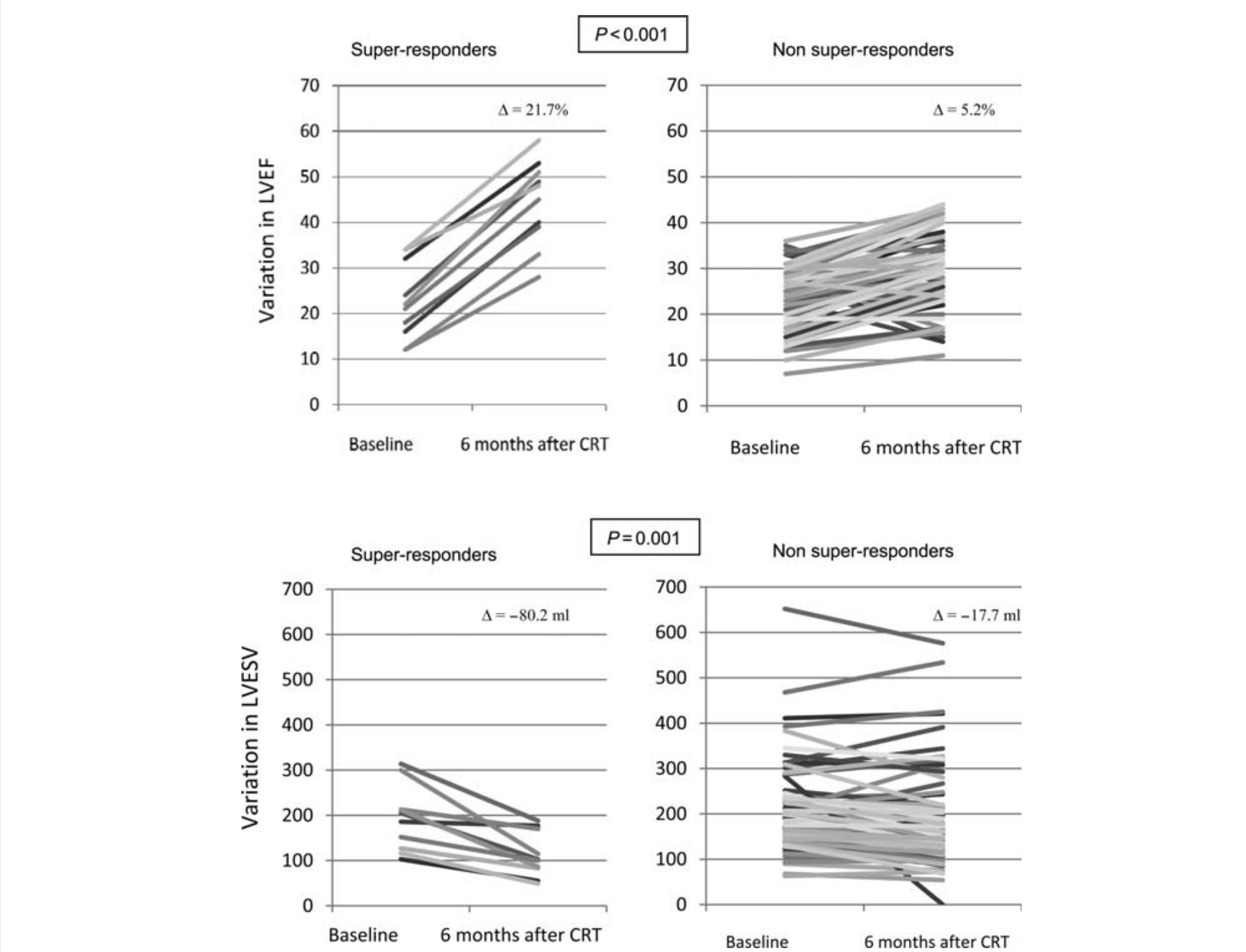

Figure 1 Comparison of the variation in left ventricular ejection fraction and left ventricular end-systolic volume between super-responders and the other patients.

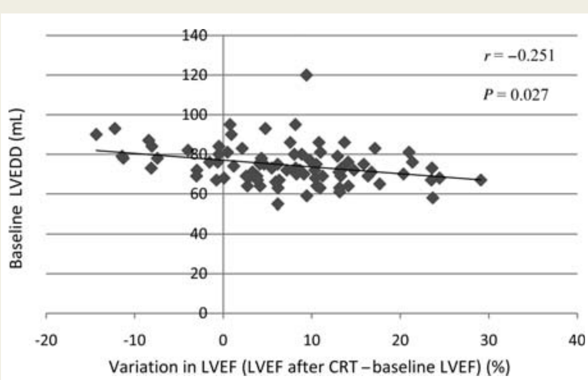

Figure 2 Correlation between baseline left ventricular diastolic diameter and variation in left ventricular ejection fraction after cardiac resynchronization therapy.

and to be more desynchronized at baseline, these parameters were not significantly different between groups and were not independent predictors of such exceptional response to CRT.

In our work, an evolution of heart failure symptoms for <12 months was an independent predictor of super-response to CRT, suggesting that resynchronization could be more efficient in the earlier phases of the disease.

Super-responders in off-label indications for cardiac resynchronization therapy

The present study demonstrated for the first time to our knowledge that this potential normalization of LV systolic function and anatomy can be achieved even in patients with AF. This is consistent with previous observations that have described a comparable CRT effect between sinus rhythm and AF groups in terms of improvement of functional capacity and LV function.[11] Likewise, narrow QRS duration or NYHA class II does not seem to prevent complete reverse remodelling. Recent studies have provided increasing evidence that CRT induced similar or even better improvement in LV function, reverse remodelling, and survival in patients with NYHA class II compared with those in NYHA class III or IV.[12,13] These findings are in favour of a beneficial effect of CRT on disease progression in patients with mild heart

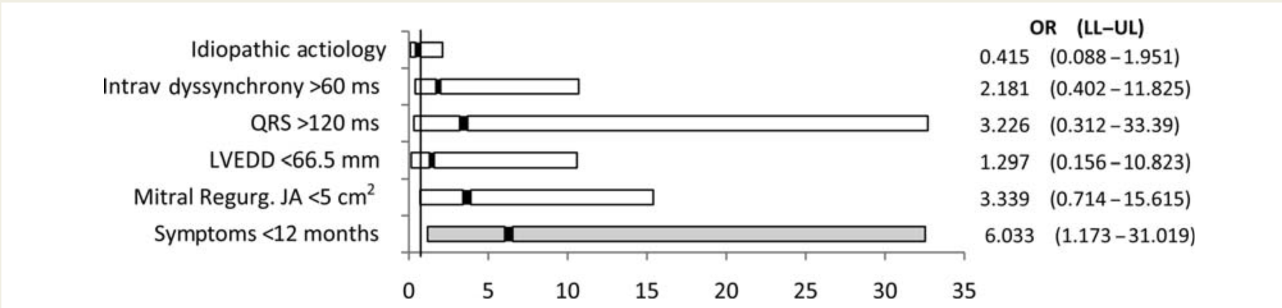

Figure 3 Multivariate logistic regression analysis for predictors of super-response to cardiac resynchronization therapy.

Table 3 Comparison of effects of cardiac resynchronization therapy in patients in New York Heart Association (NYHA) class II with patients in NYHA class III or IV

	Patients in class II (n = 9)	Patients in class III or IV (n = 78)
LVEF (%)		
Baseline	22.3 ± 5.6	24.4 ± 6.8
Follow-up	30.1 ± 6.7*	31.4 ± 9.7*
LVEDV (mL)		
Baseline	275.1 ± 66.6	263.2 ± 111.1
Follow-up	223.9 ± 77.7*	253.9 ± 124.7
LVESV (mL)		
Baseline	216.6 ± 65.5	200.9 ± 94.4
Follow-up	157.7 ± 59.4*	179.9 ± 105.0*
JA (cm^2)		
Baseline	8.1 ± 6.3	7.9 ± 5.5
Follow-up	4.1 ± 4.5*	6.1 ± 5.0*
Re-hospitalization due to heart failure (%)	0	7.7

*$P < 0.05$ follow-up vs. baseline value.

failure and may justify the possibility of having super-responders with lower baseline NYHA class. Our work further extends these findings by showing that patients with a history of <12 months of symptoms benefit the most from CRT.

To the best of our knowledge, the possibility of having super-responders even if they lack the classical indications to CRT has never been previously described.

Clinical implications

Our work demonstrated that super-responders to CRT are not rare in the real world. Additionally, these results suggest that patients with a less altered LV geometry have a higher probability of being super-responders. This may have important therapeutic implications. If confirmed by large, long-term, multi-centre studies, these results may lead to CRT in earlier phases of the cardiomyopathy when the probability of complete reverse remodelling is higher. Finally, this is the first report of super-responders in off-label indications to CRT.

Study limitations

This is a single-centre, observational cohort study. The most important limitations of this study are the small number of patients included and the relatively short period of follow-up.

Further studies with larger number of patients are warranted to confirm these results.

Conflict of interest: none declared.

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