

Long-term outcome of ‘super-responder’ patients to cardiac resynchronization therapy

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Aims

To evaluate the long-term changes of clinical and echocardiographic parameters, the incidence of cardiac events and parameters associated with late cardiac events in ‘super-responders’ to cardiac resynchronization therapy (CRT) with [CRT defibrillator (CRT-D)] or without defibrillator back-up.

Methods and results

In all consecutive patients treated with CRT in two Italian centres (Trieste and Udine) with left ventricular ejection fraction (LVEF) ≤ 0.35 at implantation (T_{imp}) and LVEF > 0.50 1 and/or 2 years (T_{norm}) after implantation, the long-term outcome and the evolution of echocardiographic parameters were assessed; factors associated with a higher risk of cardiac events, defined as hospitalization or death for heart failure (HF), sudden death, or CRT-D appropriate interventions, were also analysed. Among the 259 patients evaluated, 62 (24%) had LVEF ≥ 0.50 at T_{norm} ($n = 44$ with at 1 year, $n = 18$ at 2 years). During a mean follow-up of 68 ± 30 months, one cardiac death (for HF) and eight cardiovascular events (two hospitalization for HF and six appropriate CRT-D interventions) occurred. At the last echo evaluation (T_{fup}) performed 51 ± 26 months after T_{imp} , LVEF was < 0.50 in five patients (> 0.45 in four of them). At univariable analysis, only LV end-systolic volume evaluated at T_{fup} was associated with a higher risk of cardiac events during follow-up.

Conclusion

In ‘super-responders’ to CRT long-term outcome is excellent. However, cardiac events, mainly CRT-D appropriate interventions, can occur despite the persistence of LVEF > 0.50 . Early identification of these patients is still an unsolved issue.

Keywords

Outcome • Super-responders • Cardiac resynchronization therapy • Heart failure

Introduction

Cardiac resynchronization therapy (CRT) can improve symptoms, left ventricular (LV) function, and survival in about 70% of patients with symptomatic heart failure (HF), reduced (≤ 0.35) LV ejection fraction (EF), and wide QRS (> 120 ms), especially due to left bundle branch block (LBBB).^{1,2} There is no full agreement about the definition of clinical and instrumental improvement, as several criteria have been suggested.³ In some patients (‘super-responders’), there is an exceptional improvement after CRT leading to an apparent ‘recovery’, or ‘remission’⁴ of the LV dysfunction, with the normalization (or near-normalization) of the LVEF (> 0.50). In addition, LBBB can be considered the main cause, and not a consequence, of

LV dysfunction in some patients with the so called ‘LBBB-induced cardiomyopathy’.^{5,6} In this group, after resolution of dyssynchrony, a particular benefit from CRT could be expected.

Owing to ‘normalization’ of LV function, the need for a persistent defibrillator back-up [CRT defibrillator (CRT-D)] in ‘super-responders’ could be questionable. However, long-term follow-up studies about the group of ‘super-responder’ patients are lacking.⁷

The aim of our study was to analyse the long-term total and cardiac mortality, sudden death (SD), and CRT-D intervention rate, as well as the evolution of echocardiographic parameters in patients with LVEF > 0.50 following CRT implantation. To identify the parameters associated with a higher risk of cardiac events (cardiac mortality, aborted SD, CRT-D appropriate interventions, and HF hospitalizations),

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What's new?

- Excellent long-term outcome in super-responders to cardiac resynchronization therapy (CRT).
- Long-term persistence of normal or near-normal ventricular function in super-responders to CRT.
- Long-term risk of appropriate CRT defibrillator interventions despite good left ventricular function in some super-responders.

echocardiographic characteristics in 'super-responder' patients with and without cardiac events during the follow-up were compared.

Materials and methods

All the patients treated with CRT without defibrillator back-up [CRT pacemaker (CRT-P)] or with CRT-D at the University Hospitals of Trieste and Udine (Italy) from 1 January 2001 to 31 December 2009 have been included in two different Registries and followed long-term by their respective Arrhythmic and Heart Failure Centers.

Indication to CRT was given according to the guidelines available at the time of implantation, after discussion with the patients and referring physicians. In all the patients, LVEF was ≤ 0.35 and QRS duration was > 120 ms because of LBBB or right ventricular stimulation. Written consent for the procedure and data collection were required.

Echocardiographic data were collected just before and after CRT implantation, usually once per year. Echocardiographic examinations were performed in the Echo Laboratories of the University of Trieste and Udine by a cardiologist expert in echocardiography and reviewed by the chief of the Laboratory.

Baseline characteristics included age, gender, aetiology of HF, clinical history, medical therapy, type of CRT (CRT-P or CRT-D), New York Heart Association (NYHA) functional class, electrocardiogram (ECG) analysis (QRS duration, spontaneous cardiac rhythm, and the presence and type of heart block), and echocardiographic parameters. Left ventricular end-diastolic diameter (LVVD) and left atrium (LA) dimensions were measured according to the recommendations of the American College of Cardiology Echocardiography Committee, the American Heart Association, and the European Association of Echocardiography.⁸ Left ventricular EF was calculated by using modified Simpson's formula. The degree of mitral regurgitation (MR) was assessed semi-quantitatively (grade 0–4).^{9,10}

Before CRT implantation (T_{imp}), a complete invasive and non-invasive evaluation was performed, especially to exclude a reversible (as myocarditis) or correctable (as coronary heart disease suitable for surgical or interventional treatment) cause of LV dysfunction. Medical therapy was optimized to reach the highest tolerated dosages of angiotensin-converting enzyme inhibitors, angiotensin receptors blockers, and beta-blocking agents, at least 6 months before implantation.

Cardiac resynchronization therapy devices from all major manufacturers (Biotronik, Guidant–Boston Scientific, Medtronic, Sorin, and St Jude Medical) were used. Unipolar or bipolar endocardial leads were implanted in posterolateral or lateral veins when feasible; the anterolateral and the anterior positions (i.e. vena cardiaca magna or its collaterals) were considered suboptimal and avoided if possible. Right ventricular pacing was performed either from the apex or from the mid-septum. Selection of a specific type of device (CRT-P or CRT-D) was based according to the ongoing guidelines, patient characteristics (especially age), and

historical period (i.e. CRT-P more frequent in the first years of the decade). After implantation, tailored device reprogramming was performed before discharge only when suboptimal atrioventricular or intra-ventricular synchronization was evident at echocardiographic examination; the devices were checked at least every 6 months in all patients; reprogramming was performed in the presence of arrhythmias, clinical and echocardiographic lack of response to therapy or if the percentage of pacing was $< 95\%$.

Patient population ('super-responders') included all patients with LVEF > 0.50 at echo performed 1 year (range 9–18 months) and/or 2 years (range 18–30 months) after implantation (T_{norm}).

The clinical status of the 'super-responders' at the closure of the study (30 April 2013) was verified with the referring physician, the Heart Failure Center, the Arrhythmia Center, or directly with the patients. Cardiac death, heart transplantation, HF hospitalization, sustained ventricular tachycardia, or appropriate CRT-D interventions occurring after T_{norm} were defined as cardiac events. Clinical and echocardiographic data at the last available follow-up visit (T_{fup}) were also collected.

Finally, patients with and without cardiac events were compared at T_{imp} , T_{norm} , and T_{fup} to identify the parameters associated with a worse outcome.

Statistical analysis

Summary statistics of clinical and instrumental parameters were expressed as a mean and standard deviation or counts and percentage, as appropriate. Comparisons between groups were made by the analysis of variance test on continuous variables, using the Brown–Forsythe statistic when the assumption of equal variances did not hold, and the χ^2 test or Fisher's exact test were calculated for discrete variables. Repeated measures of continuous parameters were compared by means of the paired t-test and with the Mc Nemar test for binary variables. The results are regarded as statistically significant when $P \leq 0.05$. All calculations were performed by using IBM SPSS 19.0 for Windows.

A multivariable analysis was not feasible since the limited number of events, taking into account the number of candidate predictors in a multivariable model has to be inferior to the number of events divided by 10.¹¹

Results

From 1 January 2001 to 31 December 2009, 259 consecutive patients who underwent CRT-P or CRT-D implantation at the University Hospitals of Trieste and Udine (Italy) were re-evaluated with echocardiographic examination at T_{norm} and T_{fup} .

The study population ('super-responders') consisted of 62 patients (24%) showing LVEF ≥ 0.50 at T_{norm} ($n = 44$ at 1 year, $n = 18$ at 2 years).

Clinical data of all patients implanted in the two centres and a comparison between the study population ('super-responders') and all the other patients at implantation (T_{imp}) are summarized in Table 1; briefly, in 'super-responders', the diagnosis of idiopathic dilated cardiomyopathy was more frequent (48.7 vs. 31.3%, $P = 0.007$) and paced QRS after CRT was shorter (132 ± 23 vs. 156 ± 18 ms, $P < 0.001$); before CRT, the 'super-responders' were more symptomatic for HF than other patients (NYHA class III in 74.2 vs. 44.8%; class II 14.5 vs. 41%; $P = 0.001$), but a less degree of left atrial and ventricular dilatation was present.

In the 'super-responders' the interval between HF onset (or first detection of LV dysfunction) and CRT implantation was 40 ± 44

Table 1 Baseline clinical and echocardiographic parameters

Clinical parameters	All CRT patients (n = 259)	Super-responders (n = 62)	Other patients (n = 197)	P
Age	66 ± 10	64 ± 10	67 ± 11	0.187
BMI	26 ± 4	27 ± 4	26 ± 4	0.182
Males (%)	194 (78.5%)	44 (71%)	150 (81.1%)	0.069
NYHA class				0.001
I	5 (2.1%)	1 (1.6%)	4 (2.2%)	
II	84 (34.3%)	9 (14.5%)	75 (41.0%)	
III	128 (52.2%)	46 (74.2%)	82 (44.8%)	
IV	28 (11.4%)	6 (9.7%)	22 (12.0%)	
Aetiology				0.007
Idiopathic dilated cardiomyopathy	85 (35.7%)	30 (48.7%)	55 (31.3%)	
Ischaemic cardiomyopathy	79 (33.2%)	16 (25.7%)	63 (35.8%)	
Hypertensive cardiomyopathy	15 (6.3%)	7 (11.2%)	8 (4.5%)	
Other aetiologies	59 (24.8%)	9 (14.4%)	50 (28.4%)	
Permanent atrial fibrillation	89 (35.9%)	20 (32.3%)	69 (37.1%)	0.298
CRT without defibrillation back-up	22 (15.3%)	7 (12.7%)	15 (16.9%)	0.136
CRT with defibrillation back-up for primary prevention	109 (75.7%)	46 (83.6%)	63 (70.8%)	0.136
CRT with defibrillation back-up for secondary prevention	13 (9.0%)	2 (3.6%)	11 (12.4%)	0.136
Posterolateral stimulation	101 (82.1%)	50 (86.2%)	51 (78.6%)	0.061
Baseline QRS (ms)	167 ± 26	168 ± 18	167 ± 30	0.769
QRS after implantation (ms)	144 ± 24	132 ± 23	156 ± 18	<0.001
Echo parameters				
LVEDV (mL)	211 ± 82	181 ± 58	232 ± 89	<0.001
LVEF (%)	27 ± 8	28 ± 9	27 ± 8	0.179
LVEDD (mm)	70 ± 10	65 ± 9	73 ± 9	<0.001
LAD (mm)	47 ± 8	47 ± 8	47 ± 8	0.0737
LAA (cm ²)	29 ± 8	25 ± 7	32 ± 7	<0.001

BMI, body mass index; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LAD, left atrium diameter; LAA, left atrium area; NYHA, New York heart association.

months. Upgrading from devices with right ventricular stimulation only was performed in 15 patients (24%).

In 16 patients (26%), there was a history of coronary heart disease (15 with previous myocardial infarction). Ten patients underwent percutaneous coronary revascularization more than 6 months earlier. In 30 patients (48%), a diagnosis of dilated cardiomyopathy was performed, but in 22 patients (35%), LV was reported to be normal when LBBB was detected for the first time ($n = 14$) or before right ventricular stimulation ($n = 8$). In these patients, a diagnosis of 'LBBB-induced cardiomyopathy' was considered likely. Permanent atrial fibrillation (AF) was present in 20 patients (32%). Mean ventricular rate was 65 ± 13 b.p.m. (and lower than 90 b.p.m. in all patients) before CRT. In four patients, with mean ventricular rate >80 b.p.m., ablation of the AV node was performed just following CRT implantation to achieve 100% ventricular pacing. After CRT, mean ventricular rate in patients with AF was 66 ± 6 b.p.m.

Figure 1 and Table 2 summarize the baseline and follow-up NYHA classification and echocardiographic data from the study population.

Nineteen patients (31%) at T_{norm} and 17 patients (27%) at T_{fup} were in NYHA class II. All the other patients were classified in NYHA I class after CRT.

At T_{imp} , mean LVEF was 0.28 ± 0.09 , LVDD 65 ± 9 mm, and LV end-diastolic volume (LVDV) 181 ± 58 mL. At T_{norm} , LVEF was 0.56 ± 0.06 , LVDD 55 ± 5 mm, and LVDV 111 ± 27 mL ($P = 0.001$ vs. T_{imp} for all these parameters). At the last echocardiographic evaluation (T_{fup}), performed 51 ± 27 months after T_{imp} , a further statistically significant improvement of LV function and a reduction of LV end-systolic volume (LVSV) was observed. At T_{fup} , LVEF was <0.50 in five patients, but <0.45 (0.36) in only one patient.

A moderate MR (grade 3/4) was present in three patients before CRT implantation. In all of them there was only a mild (grade 1/4 in one patient) or no MR (in two patients) at T_{norm} and T_{fup} .

Mean follow-up of the study population was 68 ± 30 months. During this period, four patients (6%) died, three of them for non-cardiac reasons. The only cardiovascular death was observed in a 85-year-old woman, treated with CRT on 24 January 2001 and hospitalized because of 'heart failure' for the first time 6 years later

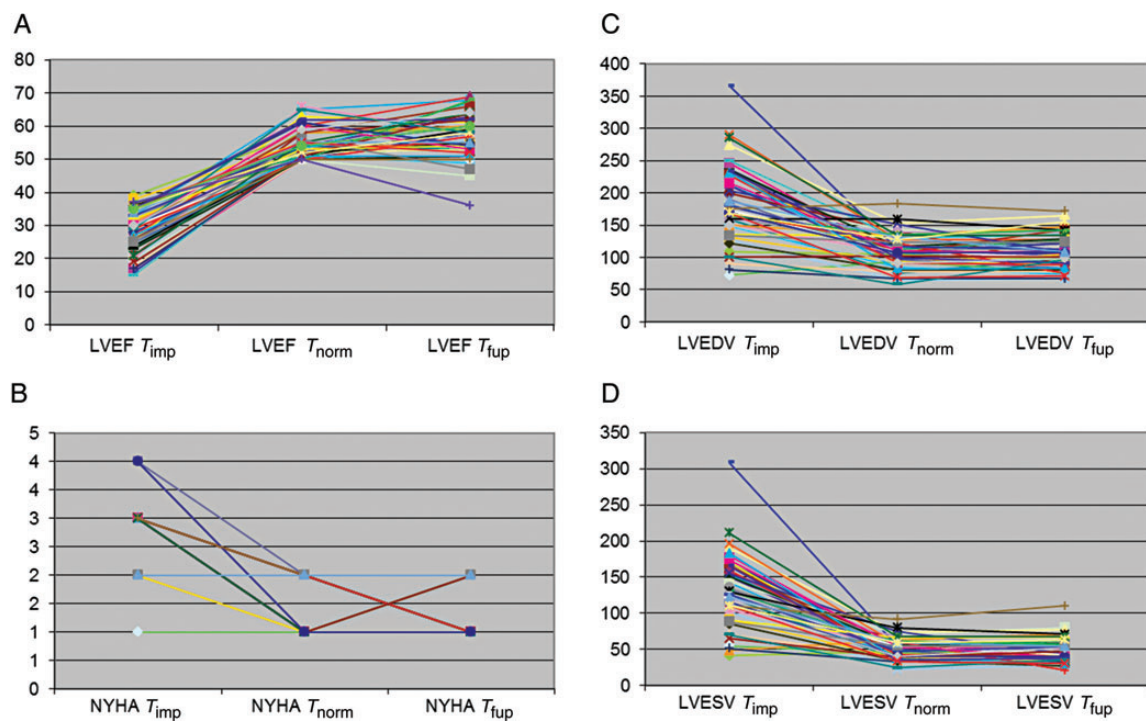


Figure 1 Clinical and echocardiographic data at implantation and during long-term follow-up. (A) LVEF at implantation (T_{imp}), after 1 or 2 years (T_{norm}) and at the last echocardiographic follow-up (T_{fup}) after 51 ± 27 months; (B) NYHA functional class at T_{imp} , T_{norm} , and T_{fup} ; (C) LVEDV at T_{imp} , T_{norm} , and T_{fup} ; (D) LVESV at T_{imp} , T_{norm} , and T_{fup} . Legend: see Table 1.

Table 2 Echocardiographic parameters

	Baseline (T_{imp})	1–2 years (T_{norm})	Last follow-up (T_{fup})	P T_{imp} vs. T_{norm}	P T_{norm} vs. T_{fup}
LVEDV (mL)	181 ± 59	112 ± 26	110 ± 29	<0.001	ns
LVESV (mL)	128 ± 49	51 ± 14	48 ± 17	<0.001	0.05
LVEF (%)	28 ± 9	54 ± 4	57 ± 6	<0.001	0.05
LVEDD (mm)	65 ± 9	55 ± 6	54 ± 6	<0.001	ns
LVESD (mm)	52 ± 12	38 ± 6	38 ± 7	<0.001	ns
LAD (mm)	47 ± 9	44 ± 8	44 ± 6	ns	ns
pts in SR	45 ± 8	42 ± 6	43 ± 6	ns	ns
pts in AF	51 ± 10	49 ± 9	48 ± 7	ns	ns
LAA (cm ²)	25 ± 7	21 ± 7	22 ± 5	0.02	ns
pts in SR	24 ± 5	20 ± 6	22 ± 5	0.013	ns
pts in AF	37 ± 10	32 ± 8	31 ± 7	ns	ns
sPAP (mmHg)	33 ± 8	29 ± 6	29 ± 7	0.033	ns
RVD (%)	3 (5%)	2 (3%)	2 (3%)	ns	ns

T_{imp} , time of implantation; T_{norm} , evaluation after 1–2 years; T_{fup} , last echocardiographic follow-up; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LAD, left atrium diameter; LAA, left atrium area; pts in SR, patients in sinus rhythm; pts in AF, patients in atrial fibrillation; sPAP, systolic pulmonary artery pressure; RVD, right ventricular dysfunction.

(October 2007); echocardiographic evaluation, performed in another hospital, was not available at that time. At the last available echo (March 2007), LVEF was 0.60, and mild MR with moderate pulmonary hypertension (estimated systolic pulmonary pressure 42 mmHg) was

detected. Finally, she died because of ‘heart failure’ (according to the hospital database) in 2010.

In eight patients (13%), the first cardiac event occurred 51 ± 30 months after T_{imp} (hospitalization for HF in two and appropriate

Table 3 Outcome (follow-up 68 ± 30 months)

Patients with cardiovascular events	8 (13%)
Interval between implant and cardiac event (months)	46 ± 28
Hospitalization for heart failure	2 (3%)
Appropriate interventions in patients with CRT-D ($n = 53$)	6 (11%)
Interval between implant and first appropriate CRT-D intervention (months)	40 ± 29
All-cause mortality	4 (6%)
Cardiovascular mortality	1 (1.5%)

CRT-D interventions in six patients) (Table 3). The interval from T_{imp} to first CRT-D appropriate intervention was 43 ± 30 months; five out of the six first appropriate interventions occurred in patients treated with CRT-D for primary prevention.

The super-responders had a significantly lower proportion of appropriate ICD interventions in comparison with other patients (7 vs. 23% at 5 years; $P = 0.005$; see Figure 2). Inappropriate interventions (for paroxysmal AF or sinus tachycardia) occurred in five 'super-responder' patients (8.5%) during follow-up. There were no acute ischaemic events during follow-up in the study population.

Among the 22 patients with a possible 'LBBB-induced cardiomyopathy', the only cardiac event observed was an appropriate CRT-D intervention 57 months after implantation.

At univariable analysis, variables evaluated at T_{imp} and T_{norm} were not significantly different between patients with and without cardiac events (Tables 4 and 5); when evaluated at T_{imp} , patients with cardiac events had more dilated LVDV (132 ± 44 vs. 108 ± 26 mL; $P = 0.052$) and LVSV (64 ± 30 vs. 47 ± 14 mL; $P = 0.03$).

Multivariable analysis was not attempted because of the small number of events.

Discussion

The main result of our analysis was the evidence of an excellent long-term prognosis in patients considered 'super-responders' to CRT, as only 1 out of 62 patients died for cardiovascular reasons during a follow-up of more than 6 years. However, major cardiac events (in particular, appropriate CRT-D interventions and hospital admissions due to HF), although significantly less frequent than in other patients, were not negligible (13% during follow-up, 7% after 5 years) despite the persistence of normal LV function in the long term.

Reverse remodelling and 'super-responders' to cardiac resynchronization therapy

The degree of response to CRT is variable, because of the different patients characteristics, implantation procedures, and definitions of improvement or normalization;^{3,5} however, reverse remodelling usually persists in the long term;¹² according to the REVERSE study, no reduction of LV function, worsening of HF symptoms, or

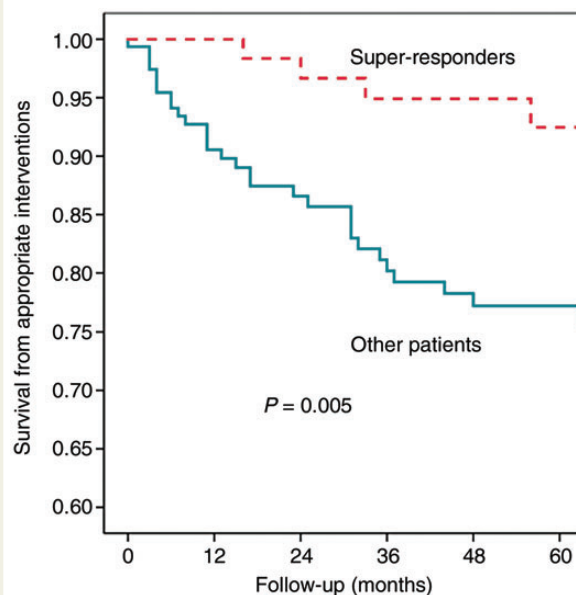


Figure 2 Survival free of appropriate defibrillator interventions in the 'super-responders' vs. other patients treated with CRT-D. Super-responders: patients with LVEF ≥ 0.50 1 or 2 years after implantation. CRT-D: cardiac resynchronization therapy with defibrillator back-up.

increase of LV volumes were evident in the 5 years following CRT implantation.¹³

Most data suggest that patients with non-ischaemic cardiomyopathy, wide QRS due to LBBB,^{7,14,15} and a shorter paced QRS¹⁴ have the greatest benefit from CRT. In our study, all the 'super-responder' patients, except those already paced from the right ventricle, had an LBBB before implantation, and QRS shortening after CRT was consistent.

A diagnosis of idiopathic dilated cardiomyopathy was more frequent in the 'super-responders' than in the other patients, confirming that in this setting reverse remodelling is more likely; however, 16 patients (26%) with ischaemic heart disease, treated with CRT more than 6 months after coronary revascularization, normalized their LV function, even in the presence of previous myocardial infarction. An accurate analysis of the parameters associated with the 'normalization' of the LV function was already performed in a previously published paper by our group and was not the aim of the present study.¹⁴

Long-term outcome in the 'super-responders' to cardiac resynchronization therapy

Echocardiographic response to CRT, more than clinical response, is associated with a lower mortality,^{16,17} but few data have been published about the long-term outcome of patients with LV normalization after CRT. In the MADIT-CRT, non-fatal HF events or all-cause death after the 12-month echocardiogram occurred in

Table 4 Baseline clinical characteristics in patients without and with cardiovascular events during follow-up

	Patients without cardiovascular events (n = 54)	Patients with cardiovascular events (n = 8)	P
Age (years)	65 ± 10	65 ± 9	ns
Weight (kg)	79 ± 15	78 ± 9	ns
Height (cm)	170 ± 8	173 ± 7	ns
Males (%)	44 (71%)	7 (88%)	ns
IDCM	28 (50%)	2 (28%)	ns
Ischaemic cardiopathy	17 (31%)	3 (38%)	ns
Hypertensive cardiopathy	7 (13%)	1 (12%)	ns
Other aetiologies	7 (13%)	2 (25%)	ns
Serum creatinine (mg/dL)	1.1 ± 0.2	1.2 ± 0.4	ns
Atrial fibrillation	17 (31%)	3 (42%)	ns
CRT-D	47 (85%)	6 (85%)	ns
Primary prevention	42 (87%)	6 (85%)	ns
Posterolateral stimulation	42 (84%)	8 (100%)	ns
Baseline QRS	169 ± 20	167 ± 15	ns
QRS stimulated	127 ± 20	128 ± 11	ns
Upgrading from RV stim	14 (24%)	1 (15%)	ns
'Pure dyssynchrony' (LBBB before the LV dysfunction)	21 (39%)	1 (16%)	ns

IDCM, idiopathic dilated cardiomyopathy; RV stim, right ventricle stimulation; LBBB, left bundle branch block; LV, left ventricle.

2.6%, all-cause death in 1.6%, and all-cause death or CRT-D therapy for ventricular tachycardia or ventricular fibrillation in 5.2% of the super-responders; however, in the MADIT-CRT, follow-up was shorter (median 15 months) and no data about long-term LV function were available.¹⁸ In addition, the definition of 'super-responders' was different (the highest quartile of LVEF change), while we included only patients with 'normalized' LV function, i.e. LVEF > 0.50, as in most published paper evaluating predictors of CRT response.⁷

Castellani et al.¹⁹ showed that, among 11 patients with LV 'normalization' (LVEF > 0.50) after CRT there was only one death, 46 months after CRT implantation, due to pulmonary embolism, in a patient with a normal heart evaluated a few weeks before death. All the other 10 remaining patients were alive during a follow-up of 50 ± 35 months.

More recently, Manne et al.²⁰ showed that long-term survival is similar in patients with 'normalization' of LVEF (>0.50) after CRT and the general population.

In our series, we found similar results, as only one patient died for HF 9 years after implantation at the age of 85.

Table 5 Echocardiographic parameters in patients without and with cardiovascular events during follow-up

	Patients without cardiovascular events (n = 54)	Patients with cardiovascular events (n = 8)	P
<i>T_{imp}</i>			
LVEDV (mL)	180 ± 59	191 ± 54	ns
LVESV (mL)	128 ± 48	130 ± 57	ns
LVEF (%)	28 ± 6	34 ± 18	ns
LVEDD (mm)	65 ± 9	66 ± 6	ns
LVESD (mm)	53 ± 10	44 ± 19	ns
LAD (mm)	47 ± 9	49 ± 10	ns
LAA (cm ²)	25 ± 7	27 ± 7	ns
sPAP (mmHg)	33 ± 8	35 ± 10	ns
<i>T_{norm}</i>			
LVEDV (mL)	109 ± 25	132 ± 31	0.06
LVESV (mL)	50 ± 13	62 ± 16	0.06
LVEF (%)	55 ± 4	53 ± 2	ns
LVEDD (mm)	55 ± 6	55 ± 6	ns
LVESD (mm)	38 ± 6	38 ± 5	ns
LAD (mm)	44 ± 8	48 ± 6	ns
LAA (cm ²)	22 ± 8	22 ± 6	ns
sPAP (mmHg)	29 ± 5	30 ± 10	ns
<i>T_{fup}</i>			
LVEDV (mL)	108 ± 26	132 ± 44	0.052
LVESV (mL)	47 ± 14	64 ± 30	0.03
LVEF (%)	57 ± 6	53 ± 10	ns
LVEDD (mm)	54 ± 5	55 ± 11	ns
LVESD (mm)	38 ± 6	38 ± 12	ns
LAD (mm)	44 ± 7	47 ± 4	ns
LAA (cm ²)	22 ± 6	24 ± 2	ns
sPAP (mmHg)	29 ± 7	34 ± 6	ns

T_{imp}, time of implantation; *T_{norm}*, evaluation after 1–2 years; *T_{fup}*, last echocardiographic follow-up; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LAD, left atrium diameter; LAA, left atrium area; sPAP, systolic pulmonary artery pressure.

Cardiac resynchronization therapy-defibrillator or cardiac resynchronization therapy-pacemaker in the 'super-responders' at device replacement?

Reverse remodelling is associated with a reduction of the risk of ventricular arrhythmias.^{21,22} Cardiac resynchronization therapy partially restores the electrophysiological remodelling due to dyssynchronous LV contraction, abnormal calcium homeostasis, and regional heterogeneity of action potential duration, possibly reducing ventricular arrhythmias.²³ According to the Task Force of several American Scientific Associations on the appropriate use criteria for Implantable Cardioverter-Defibrillators and Cardiac Resynchronization Therapy,²⁴ in patients with CRT-D and LVEF ≥ 0.50 at the time of elective replacement, a CRT-D 'is' appropriate (with an appropriate use score of 7/9) but even a downgrading to CRT-P 'may be' appropriate (with an appropriate use score of 6/9).

In the recently published paper by Van Boven *et al.*²⁵, no appropriate CRT-D interventions were observed in patients with 'functional response' to CRT (i.e. LVEF > 0.35 4 months after implantation).

Although we included only those with LVEF ≥ 0.50 after CRT in our study, at least one appropriate CRT-D intervention occurred in 5 out of the 53 patients with CRT-D (4 treated for primary prevention). The different results could be explained by a greater number of patients but especially a longer follow-up in our population; in fact, the first intervention occurred on average 43 months after implantation in our patients, while the median follow-up was < 3 years in the series described by Van Boven *et al.*²⁵ According to Manne *et al.*,²⁰ there were three appropriate interventions among the 67 'super-responder' patients during follow-up. In that study, however, there was a drop of LVEF before the appropriate interventions, while in all our patients LVEF was still normal in the 6 months prior to the CRT-D intervention or even after the event.

Therefore, according to our data, the risk of significant ventricular tachyarrhythmias was not completely eliminated by the 'normalization' of LV function among 'super-responders' in the long term. This could have several potential explanations: first of all, despite echocardiographic improvement, a complete recovery is unlikely in these patients and the term 'remission' should be more appropriate,⁴ as the pathological substrate can be still present²⁶ and electrical reverse remodelling not complete after CRT.²⁷ Some data suggest that in the very long-term (> 10 years) patients with idiopathic dilated cardiomyopathy considered 'apparent healed' just on optimal medical treatment can worsen again their LV function,²⁸ suggesting that the improvement, although long-lasting, can be transient, or not complete. Finally, other potential precipitating factors (transient electrolyte imbalance, silent ischaemic events, etc.) could not be excluded, although not detected, in our population.

Although appropriate interventions should not be considered a surrogate of aborted SD,²⁹ and no SD were reported among the 23 patients treated with CRT-P only, according to our data the downgrading from CRT-D to CRT-P should be advised with caution at device replacement in the 'super-responders', even in the absence of documented previous major ventricular arrhythmias.

Long-term outcome in patients with 'left bundle branch block-induced cardiomyopathy'

In 22 patients (35% of our population), LV was reported to be normal before right ventricular stimulation or when LBBB was first detected; although an initial cardiomyopathy with early abnormalities of the conduction system could not be excluded, the diagnosis of a reversible 'LBBB-induced cardiomyopathy' was likely in this group.^{5,6} In only one of these patients, a cardiovascular event (an appropriate CRT-D intervention nearly 5 years after implantation) and no cardiovascular deaths were observed during follow-up. According to Vaillant *et al.*,⁶ no deaths or major adverse clinical events (including hospitalization for management of HF) were reported, over a mean follow-up of 36 months, in six patients with > 5 -year history of typical LBBB, LVEF > 0.50 at the time of diagnosis of LBBB, progressive decrease in LVEF to ≤ 0.40 who were the super-responders (LVEF > 0.45) to CRT. No appropriate interventions were reported in their three patients with CRT-D.

Cardiac resynchronization therapy and atrial fibrillation

Permanent AF was present in a surprising high proportion of 'super-responders' ($n = 20$, 32%). However, a diagnosis of 'tachycardia-induced cardiomyopathy' was unlikely in all of them as rest ventricular rate was < 90 /min even before implantation and only four patients required AV node ablation to ensure 100% ventricular pacing, confirming that optimization of medical treatment was adequate before CRT.

Long-term clinical and echocardiographic data

Although no 'super-responder' patients were in NYHA class III or IV at T_{norm} and T_{fup} , not all patients were considered completely asymptomatic during follow-up, as many were classified in NYHA class II (Figure 1) and two patients were later hospitalized for 'heart failure' according to the hospital database. However, the limited and subjective value of the NYHA functional class for the classification of HF symptoms is well recognized.³⁰

At the last echo evaluation (T_{fup}) performed on average > 4 years after implantation, mean LVEF and LVEDV were further improved since T_{norm} , suggesting that reverse LV remodelling can continue in the long term; more importantly, in only one patient LVEF was < 0.45 at T_{fup} , confirming the persistence of long-term improvement.

Left atrial dimension is considered to be a good predictor of LV normalization after CRT.^{18,31} Not surprisingly, LA was only slightly dilated, at least in patients in sinus rhythm, at T_{imp} and normalized after CRT. A moderate dilatation was evident both at implantation and during follow-up only in patients with permanent AF.

Predictors of cardiac events among the 'super-responders'

The identification of the 'super-responders', who could still be considered at higher risk of cardiac events during follow-up is an unexplored field. As nearly all patients maintained normal LV function,

detection of echocardiographic parameters associated with cardiac events (mainly appropriate CRT-D interventions) was unlikely; nevertheless, patients with events had significantly larger LV volumes at the last follow-up echo at univariable analysis. At the moment, an explanation of this finding would be speculative, but a less complete reverse remodelling in these patients could be hypothesized.

In more than one-fourth of our patients, a history of coronary heart disease was present, cardiac events, especially CRT-D interventions, could be due to an acute coronary episode; however, the aetiology of LV dysfunction was not associated with a different incidence of cardiac events at univariable analysis. In addition, no acute ischaemic events were documented during follow-up in our population.

Owing to the little number of events, a multivariable analysis could not be performed.¹¹

Strengths and limitations of the study

The long-term clinical and echocardiographic follow-up in our population of 'super-responder' patients is probably the major strength of our study.

In our analysis, as in most published series,^{7,24} patients were considered 'super-responders' when LVEF was ≥ 0.50 after CRT. According to the recommendations of the European Society of Cardiology,⁸ however, the term 'normalization' of LV function should be used only in those with LVEF ≥ 0.55 .

The improvement of LV function is usually observed soon after CRT implantation.³² However, in our experience and according to other studies⁷ including the REVERSE,¹³ a further improvement of LVEF could be sometimes reached later during follow-up; for this reason, we decided to include also those with LVEF ≥ 0.50 detected up to 2 years after implantation (29% of our patient population). This can explain the high proportion of 'super-responders' (24%), a value observed only in a few other studies.⁷

Left atrial dimensions were evaluated by measuring the end-systolic anteroposterior diameter and four-chamber view area;⁸ data about left atrial volume were not always available, especially in less recently diagnosed patients, so were not reported.

The analysis of parameters predicting cardiac events in our population was difficult because of the low number and different type of events; therefore, we performed only univariable analysis, while multivariable analysis was not feasible.¹¹

Other parameters (Holter ECG, T-wave alternans analysis, brain natriuretic peptide dosage, cardiopulmonary test, heart-to-mediastinum ratio of meta-iodobenzylguanidine uptake, cardiac magnetic resonance, etc.) were performed before CRT implantation, but not systematically in all patients, so could not be considered for any analysis.

Conclusions

In patients treated with CRT presenting an exceptional improvement of LV function (LVEF ≥ 0.50), the long-term outcome is excellent. However, some cardiac events, mainly CRT-D appropriate interventions, can occur several years after implantation, despite the persistence of a normal or near-normal LV function. An early identification

of these patients is difficult: a lower degree of long-term reverse remodelling could be associated with a higher risk of events. According to our data, in patients with CRT-D undergoing device replacement a 'downgrading' to CRT-P should be considered with caution.

Conflict of interest: none declared.

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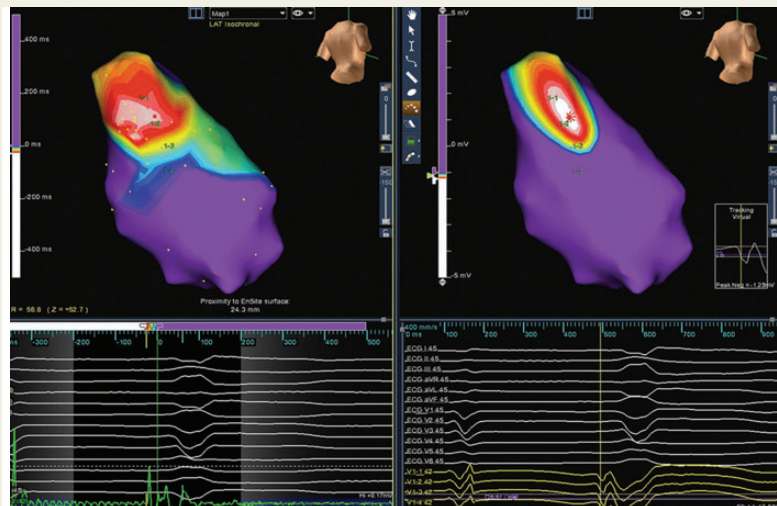
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Validation of non-contact and point-to-point mapping in a single electroanatomic map

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Non-contact mapping is often used to identify the origin of focal arrhythmias; however, validation against point-to-point mapping technologies has been limited to the construction of separate complementary maps. Recent advances (Esite Precision) have permitted single map validation of non-contact mapping using unipolar virtual endocardial electrograms with isopotential maps and point-to-point mapping using isochronal maps of activation time. This figure demonstrates mapping and validation of the area of earliest activation of a posterior right ventricular outflow tract premature ventricular contraction using both point-to-point activation mapping (red square, left panel) and non-contact isopotential mapping with a 64-electrode array (red asterisk, right panel) in the same electroanatomic map.



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