Effect of Cardiac Resynchronization Therapy on Left Ventricular Diastolic Function: Implications for Clinical Outcome

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ABSTRACT

Background: The definition of response to cardiac resynchronization therapy (CRT) remains controversial, with variable rates of response depending on the criteria used. Our aim was to analyze the impact of CRT on diastolic function in different degrees of response, particularly in patients with positive clinical but no echocardiographic response.

Methods and Results: In 250 CRT patients clinical evaluation and echocardiography were performed before and after CRT. Absolute response to CRT was defined as a reduction in left ventricular (LV) end-systolic volume of ≥15% at 1-year follow-up. Additionally, patients were classified into 4 subgroups according to their amount of response: extensive reverse remodeling (RR), slight RR, clinical response without RR, and neither clinical response nor RR. An improvement in estimates of LV filling pressure and a decrease in left atrial dimensions were observed only in responders to CRT. Patients with clinical but no echocardiographic response had significant improvement in E-wave and deceleration time and nonsignificant improvement in other parameters.

Conclusions: LV diastolic function improves with CRT. Clinical responders without echocardiographic response show improvement in parameters of diastolic function. That suggests that clinical-only response to CRT is secondary to a real effect of the therapy, rather than a placebo effect. (*J Cardiac Fail 2013;19:795−801*)

Key Words: Resynchronization, echocardiography, diastolic function, clinical response.

Cardiac resynchronization therapy (CRT) has consistently demonstrated a benefit in patients with wide QRS, reduced ejection fraction (EF), and advanced heart failure (HF), and its effects on systolic function have been extensively investigated.

However, its effects on diastolic function are scarcely studied.[1] Some studies suggest improvement in left ventricular (LV) filling pressures in responder patients,[2,3] whereas in other studies this effect was less clear.[4,5] Indeed, one of the potential abnormalities amenable to be corrected with CRT would be alteration in LV filling.[6] On the other hand, definition of response to CRT remains a subject of controversy, and this lack of a standardized parameter explains the variable rate of nonresponse reported (25%−50% depending on the response criteria used).[7] According to clinical parameters, ∼30% of patients are nonresponders; this rate may be ∼50% according to echocardiographic criteria.[8,9] Although LV volume reduction with CRT has been linked to improved survival,[10] there is poor agreement between different methods to define response,[7,11] with ∼20%−25% of patients experiencing a clinical benefit without a concomitant echocardiographic response.[9,12,13] The reasons that some patients improve clinically without a significant increase in LV ejection fraction (LVEF) or a reduction in LV volumes remain mainly unknown.

The objectives of the present study were: 1) to investigate the effect of CRT in diastolic function in our population; and 2) to analyze the effect of CRT on diastolic function in different degrees of response, particularly in patients with positive clinical but no echocardiographic response.

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Methods

The study population consisted of 250 patients undergoing CRT device implantation, as indicated under current international guidelines to include an LVEF ≤35%, QRS ≥120 ms, and New York Heart Association (NYHA) functional class II–IV despite optimal medical therapy for ≥2 months. Exclusion criteria were permanent atrial fibrillation, presence on heart transplantation waiting list, or a significant comorbidity that shortened life expectancy. The study protocol was accepted by our hospital's Ethics Committee and conformed to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from every subject.

The study protocol included a baseline clinical and echocardiographic examination, which was repeated at 1-year follow-up. Clinical evaluation included NYHA functional class assessment and a 6-minute walk test.

Device Implantation

Patients received a CRT-pacemaker or a CRT-defibrillator according to clinical indications. One lead was placed at the apex of the right ventricle, another was implanted through a distal cardiac vein into the posterolateral wall (or if necessary in the most laterally located available vein), and a third was placed in the right atrium. The coronary sinus was catheterized with the use of a guiding catheter. All leads were implanted transvenously.

Echocardiography Protocol

A comprehensive echo Doppler examination (Vivid 7; General Electric, Milwaukee, Wisconsin) was performed before initiating CRT and at 1-year follow-up. The echocardiographic exam included 2-dimensional grayscale images, color and spectral Doppler images, and tissue Doppler imaging. Three cardiac cycles were obtained for each acquisition. All studies were stored and post-processed offline with the use of commercially available software (Echopac; General Electric). LV end-diastolic and end-systolic diameters, as well as left atrial (LA) anteroposterior diameter, were measured from M-mode echocardiography in the parasternal long-axis view; LV end-diastolic and end-systolic volumes and ejection fraction were quantified with the use of the Simpson method.

LV Diastolic Function and Filling Pressures Evaluation

Diastolic function was evaluated according to current recommendations.[14] Mitral inflow velocities were studied with the use of pulsed-wave Doppler in the 4-chamber view, placing the sample volume at the tip of the mitral leaflets. The peak early filling velocity (E-wave), peak atrial filling velocity (A-wave), E-wave deceleration time (DT), and E/A ratio were calculated. The LV filling time was measured from the onset of the E-wave to the end of the A-wave, and the R-R interval was measured to calculate the percentage of filling time relative to the cardiac cycle.

Pulmonary venous flow was assessed in the 4-chamber view by placing the pulsed-wave Doppler sample volume in the right upper pulmonary vein. The peak systolic (S) velocity, peak diastolic (D) velocity, and S/D ratio were calculated.

If tricuspid regurgitation was present at both baseline and follow-up, systolic pulmonary arterial pressure (PAP) was calculated by measuring the peak velocity of the tricuspid regurgitant jet and adding an estimated right atrial pressure.

The early diastolic annular velocity (Em) was obtained with the use of tissue Doppler imaging and placing the sample volume at the mitral lateral annulus. The ratio E/Em was calculated as a measure of LV filling pressure. Finally, LA volume was calculated in the 4- and 2-chamber views according to the multiple disc summation method.

Diastolic function was classified as normal (grade 0), impaired relaxation (grade 1), pseudonormal filling (grade 2), and restrictive (grade 3), with the use of the E/A ratio and the DT as an initial evaluation. A pattern was categorized as grade 1 if the E/A ratio was <1 and the DT >240 ms, and grade 3 if the E/A ratio was >2 and the DT <160. When intermediate values were present, the pulmonary venous flow and the E/Em were used to differentiate between a pseudonormal and normal pattern.[14]

Follow-Up

At 12 months after device implantation, patients received a clinical and echocardiographic evaluation. The absolute echocardiographic response to CRT was defined as a reduction of LV end-systolic volume (LVESV) of ≥15% at follow-up. Clinical response was defined as either an increase of ≥20% in the distance walked at the 6-minute walk test or, if that test was not performed, an improvement of ≥1 NYHA functional class compared with baseline, in the absence of death or heart transplantation.

Mortality data were collected by reviewing outpatient clinical history or by phone interviews with relatives. Two cardiologists reviewed the data and by consensus assigned the mode of cardiac death. Deaths were categorized as cardiac, noncardiac, or unknown. Cardiac deaths were classified as sudden (not preceded by HF or ischemic symptoms) or due to HF. When the cause of death could not be determined, it was classified as unknown. The mean follow-up was 50 ± 27 months.

Extent of Response

Considering the difficulty of classifying response to CRT as a dichotomous variable, and to analyze the relationship between changes in LV filling pressures and diastolic function and the extent of response achieved with CRT, we created 4 subgroups of patients based on clinical and echocardiographic evolution at 1-year follow-up, in addition to the traditional criteria to define response (reduction of LVESV ≥15% at follow-up). The extent of decrease in LVESV was divided into tertiles, obtaining different reverse remodeling cutoff values. The subgroups were: 1) patients with reverse remodeling in the first tertile and no clinical response (ECHO−/CLIN−); 2) patients with reverse remodeling in the first tertile and clinical response (ECHO−/CLIN+); 3) patients with reverse remodeling in the second tertile (ECHO+); and 4) patients with reverse remodeling in the third tertile (ECHO++).

Statistical Analysis

Continuous baseline variables were expressed as mean ± SD or median (interquartile range) after checking for normality with the use of the Shapiro-Wilks test. Categoric variables were expressed as total number (percentage) and compared between groups with the use of the chi-square or Fisher test when appropriate. Continuous variables were tested by unpaired *t* test or Mann-Whitney *U* test, according to normality, and paired data by paired *t* test or Wilcoxon analysis. Kaplan-Meier curves were constructed to evaluate survival in the different subgroups of extent of response. Statistical significance was defined as $P < .05$. All data were analyzed with the use of the SPSS 15.0 statistical package (SPSS, Chicago, Illinois).

Table 1. Baseline Characteristics of the Studied Population

Age (y)	67.2 ± 2
Female	66 (26.4%)
Ischemic etiology	113 (45.2)%
NYHA functional class	
II	67 (26.8%)
III	170 (68%)
IV	13 (5.2%)
6-min walk test (m)	294.5 ± 526.4
Quality of life score	41.9 ± 99.8
Creatinine (mg/dL)	1.3 ± 3.5
QRS (ms)	170.7 ± 70.3
LVEDV (mL)	238.9 ± 97.2
LVESV (mL)	182.7 ± 76
LVEF (mL)	24.6 ± 6.6
E (cm/s)	74.4 ± 40.7
E/A	1.2 ± 2.9
DT (ms)	195.3 ± 31.3
FT (ms)	418.4 ± 434.3
FT (%)	44.4 ± 4.8
Em (cm/s)	7.1 ± 1
E/Em	12.1 ± 1.9
LA AP diameter (mm)	47.1 ± 1
LA volume (mL)	84.4 ± 44.5
S/D	1.1 ± 1.6
Systolic PAP (mm Hg)	39.6 ± 62.3

NYHA, New York Heart Association; 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; E, peak E velocity; DT, deceleration time; FT, filling time; Em, early diastolic annular velocity; LA, left atrial; AP, anteroposterior; S/D, ratio between peak systolic and diastolic velocities in the pulmonary vein; PAP, pulmonary arterial pressure.

Results

The baseline characteristics of the studied population are summarized in Table 1. Of the 250 patients included, 136 (54.4%) responded to CRT at 1-year follow-up according to the absolute echocardiographic response criteria, whereas 114 (45.6%) were nonresponders.

LV volumes and LVEF significantly improved after 1 year with CRT in the responder group, whereas increased LV end-diastolic volume and LVEF were observed in nonresponders (see Table 2).

Diastolic Function, LV Filling Pressures, and Echocardiographic Response to CRT

At 1-year follow-up, a significant decrease in the values of E, E/A, and E/Em and an increase in DT and filling time were observed in the echocardiographic responder group; LA dimensions (diameter and volumes) also significantly decreased. In nonresponders, Em decreased and DT and E/Em increased at 1-year follow-up, without significant changes compared with baseline in any of the other parameters assessed (Table 2). Figure 1 shows the degree of LV diastolic dysfunction at baseline and at 1-year follow-up in nonresponders to CRT (Fig. 1A) and in responders to CRT (Fig. 1B) as defined by reduction in LVESV ≥15%. In the nonresponder group, 24 patients (21%) showed worsening of degree of LV diastolic function, which occurred in only 1 patient in the responder group. Conversely, the degree of diastolic dysfunction improved in 47 responder patients (34%) at follow-up, in contrast to only 22 nonresponder patients (19%). In most responders, the diastolic pattern was abnormal relaxation at baseline (n = 75; 55%) and at follow-up (n = 113; 83%).

A significant reduction in the systolic PAP also was observed in responders (40.3 ± 32.7 vs 34.2 ± 2.6 mm Hg; $P < .0001$), whereas no significant changes were seen in nonresponders (40.8 ± 82.7 vs 39.8 ± 80.6; P = ns).

Extent of Response

The extent of decrease in LVESV at 1-year follow-up was divided into tertiles, obtaining different reverse remodeling cutoff values: reduction of LVESV >30.5% versus baseline; reduction of LVESV from 30.5% to 7.5%; and volumetric reduction <7.5% or LVESV increase at follow up. The 4 subgroups defining the extent or amount of response were constituted thus: 1) LVESV reduction >30.5%

Table 2. Diastolic Function According to Echocardiographic Response (Reduction of LVESV ≥15%)

	Responders (n = 136; 54.4%)		Nonresponders (n = 114; 45.6%)	
	Baseline	1 y	Baseline	1 y
LVEDV (mL)	236.5 ± 59.5	178.6 ± 64.3*	242.4 ± 45.1	253.3 ± 38.1†
LVESV (mL)	183.1 ± 16.7	114.3 ± 39.2*	183.2 ± 25.8	188.7 ± 78.8
LVEF (%)	24.1 ± 1.7	38.2 ± 2.1*	25.2 ± 2.6	27.3 ± 3.4†
E (cm/s)	74.9 ± 92.4	63.2 ± 22.6*	74.2 ± 27.5	71 ± 16.3
E/A	1.1 ± 1.8	0.9 ± 9.5*	1.3 ± 3	1.4 ± 4.3
DT (ms)	200.8 ± 86.8	245.6 ± 65.1*	191.7 ± 74.9	209.5 ± 51.2†
FT (ms)	396.9 ± 924.8	502.9 ± 950.5*	447.9 ± 947.6	445.4 ± 434.6
FT (%)	42.9 ± 9.9	49.7 ± 7.9*	46.3 ± 31.4	47.2 ± 2.9
Em (cm/s)	6.8 ± 8.8	7 ± 7.9	7.7 ± 7.9	6.7 ± 7.1†
E/Em	12.8 ± 8.1	10.4 ± 4.4*	10.9 ± 9.1	13.5 ± 5.5†
LA AP diameter (mm)	45.9 ± 9	43.5 ± 5.2*	47.6 ± 6.9	47.9 ± 9.8
LA volume (mL)	77.3 ± 39.7	70.2 ± 27.2*	97.5 ± 57.6	100.5 ± 50.9
S/D	1.3 ± 3.6	1.9 ± 9.9	1 ± 1.6	1.2 ± 2.5
Systolic PAP (mm Hg)	40.3 ± 32.7	34.2 ± 2.6*	40.8 ± 82.7	39.8 ± 80.6

Abbreviations as in Table 1.
*$P < .01$ vs responders at baseline.
†$P < .05$ vs nonresponders at baseline.

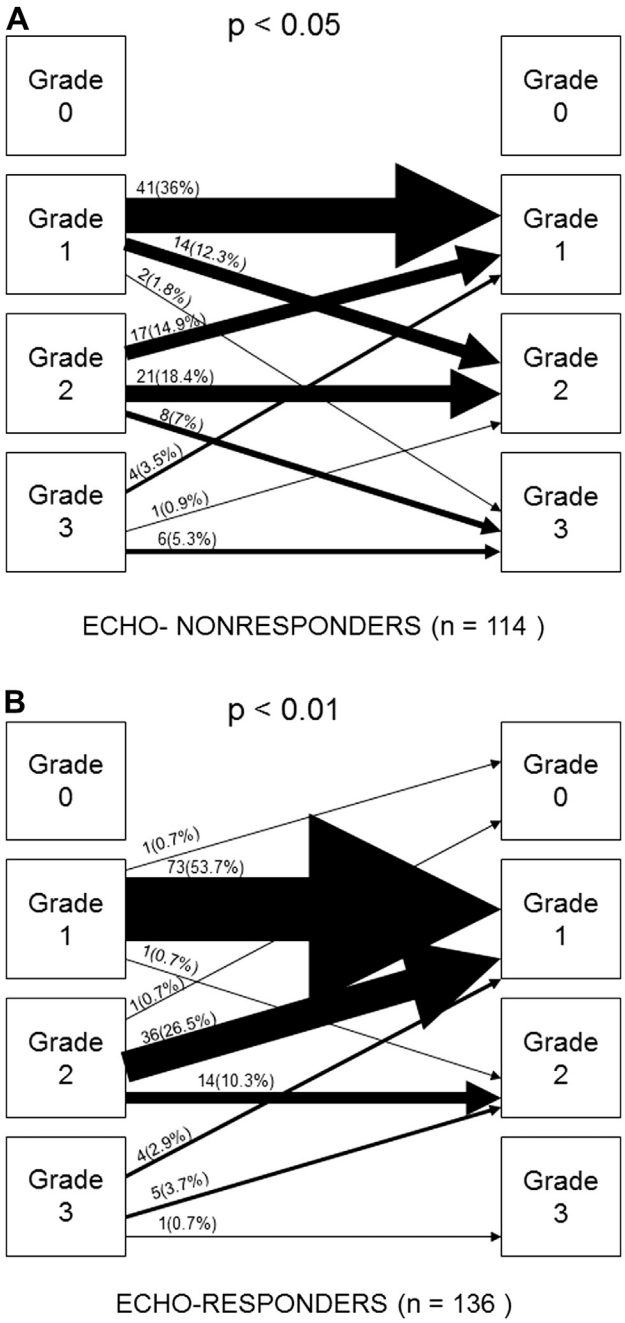

Fig. 1. (A) Degree of left ventricular (LV) diastolic dysfunction at baseline and at 1-year follow-up in nonresponders to cardiac resynchronization therapy (CRT) as defined by a reduction in LV end-systolic volume of ≤15%. (B) Degree of LV diastolic dysfunction at baseline and at 1-year follow-up in responders to CRT as defined by a reduction in LV end-systolic volume of ≥15%. The thickness of the arrows correlates with the number of patient in each situation.

(ECHO++ response); 2) LVESV reduction from 7.5% to 30.5% (ECHO+ response); 3) LVESV reduction <7.5% but with positive clinical response (ECHO−/CLIN+ response); and 4) LVESV reduction <7.5% without clinical response (ECHO−/CLIN− response) or the occurrence of death or heart transplantation at 1-year follow-up. No significant differences in standard HF medication were observed between the subgroups, except for the presence of beta-blockers, which were used in 61 (77.2%) of the ECHO++ subgroup, 57 (69.5%) of ECHO+, 32 (57.1%) of ECHO−/CLIN+, and 12 (42.9%) of ECHO−/CLIN− (P = .004). The subgroup of patients with the lowest percentage of beta-blockers (ECHO−/CLIN−) comprised patients with a worse clinical baseline status in whom the treatment with beta-blockers was not tolerated; this subgroup had a higher creatinine serum level compared with ECHO−/CLIN+, ECHO+, and ECHO++ (1.4 ± 4.5 vs 1.3 ± 3.6 vs 1.3 ± 3.4 vs 1.1 ± 1.4, respectively; P = .001) and larger LV volumes (LV end-diastolic volume 258.7 ± 71.1 vs 233.9 ± 98.9 vs 247.9 ± 93.1 vs 227.3 ± 38.3 [P = .386]; and LVESV 193 ± 32.3 vs 178 ± 88.4 vs 190.2 ± 20.3 vs 176.3 ± 38.2 [P = .628]).

These results are summarized in Tables 3 and 4. A progressive improvement of all the assessed parameters of LV diastolic function and estimates of LV filling pressures was observed with greater extent of reverse remodeling. Although patients without any kind of response (neither echocardiographic nor clinical) demonstrated a significant worsening of E/Em and a worsening trend for the remaining parameters estimating LV diastolic function and filling pressures, those patients with extensive reverse remodeling showed significant improvements in most of the studied parameters. These changes were observed together with a progressive reverse remodeling of the LA with reduction in its dimensions. Finally, the progressive changes in LV diastolic function, LV filling pressures, and LA reverse remodeling paralleled LV reverse remodeling and improvement in LV systolic function.

Interestingly, those patients without significant reverse remodeling but with a positive clinical response showed significant improvement in E wave velocity and DT values and a nonsignificant trend toward improvement in degree of diastolic dysfunction, systolic PAP, E/A, S/D, and filling time. This particular subgroup of patients had a higher proportion of patients with cardiomyopathy of ischemic etiology and patients in NYHA functional class IV compared with the subgroups with some degree of reverse remodeling after CRT (ischemic etiology: 32 (57.1%) vs 68 (41%), respectively; NHYA IV: 7 (12.5%) vs 5 (3%); both P < .05).

To analyze whether patients with ECHO−/CLIN+ response had a different prognosis compared with nonresponders, we studied long-term mortality in the 4 subgroups of patients. Whereas patients with some degree of reverse remodeling (ECHO++ and ECHO+ response) had a better survival at long-term follow-up than patients with ECHO−/CLIN− response, no significant differences were observed in survival between patients with ECHO−/CLIN− or ECHO−/CLIN+ responses. However, when analyzing the Kaplan-Meier curves, an initial slight difference on survival between the latter subgroups could be observed, which was lost at long-term follow-up (Fig. 2).

Table 3. Extent of Response and Left Ventricular Diastolic Function and Filling Pressure Estimates

	Nonresponders (n = 28; 11.2%)		Clinical Responders (n = 56; 22.4%)		Slight RR (n = 84; 33.6%)		Extensive RR (n = 82; 32.8%)	
	Baseline	1 y	Baseline	1 y	Baseline	1 y	Baseline	1 y
QRS (ms)	167.7 ± 78.9	143 ± 38.6*	174 ± 46.8	140.7 ± 72.2*	168.5 ± 58.9	144.5 ± 53.3*	171.6 ± 67.3	140.8 ± 86.8*
LVEDV (mL)	258.7 ± 71.1	282 ± 29.9*	233.9 ± 98.9	252.6 ± 69.9*	247.9 ± 93.1	223.7 ± 77.4*	227.3 ± 38.3	150.8 ± 81.5*
LVESV (mL)	193 ± 32.3	214.3 ± 39.4*	178 ± 88.4	191.2 ± 20.8*	190.2 ± 20.3	153.4 ± 42.6*	176.3 ± 38.2	91.8 ± 80.6*
LVEF (%)	24.9 ± 9.2	26.1 ± 1.6	25.3 ± 3.9	26.7 ± 7	24.6 ± 6.1	32.4 ± 4.5*	24 ± 4.3	40.9 ± 9.4*
E (cm/s)	69.5 ± 54.4	76.1 ± 10.2	75.3 ± 38.4	67.5 ± 54.1*	76.6 ± 60	68.5 ± 58.1*	74.3 ± 33.4	61.6 ± 61.4*
E/A	1.2 ± 2	1.3 ± 3.9	1.4 ± 4	1.3 ± 3	1.4 ± 4	1.2 ± 2.3	0.9 ± 9.7	0.8 ± 8.4
DT (ms)	200.1 ± 13.7	188.4 ± 47.6	182.5 ± 52.2	215.1 ± 17.9*	200.6 ± 65.9	226.6 ± 62.9*	201.6 ± 66.5	255.6 ± 64.9*
FT (%)	46.4 ± 43.4	47.8 ± 8.3	46.1 ± 10.7	49.1 ± 1.4	43.7 ± 7.7	47.5 ± 50.9*	43 ± 3.4	49.9 ± 9.7*
Em(cm/s)	7 ± 7	6.1 ± 1.9	8.1 ± 1.9	6.9 ± 9.4	7.1 ± 1.7	6.6 ± 6.9	6.8 ± 8.9	7.3 ± 3.8
E/Em	11.1 ± 1.2	14.7 ± 7.1*	10.5 ± 5.9	12.1 ± 1.2	13.1 ± 1.2	12.6 ± 6.9	12.3 ± 3.6	9.6 ± 6.3*
LA AP Ø (mm)	46.6 ± 6.5	48.5 ± 5.6	47.7 ± 7	47.7 ± 7.5	47.9 ± 9.5	47 ± 7.1	44.7 ± 7.3	41.6 ± 6.3*
S/D	1.2 ± 2.5	1.1 ± 1.5	1 ± 1.6	1.2 ± 2.6	1.1 ± 1.6	1.1 ± 1.5	1.3 ± 3.6	1.4 ± 4.4
sPAP (mm Hg)	36.5 ± 5.2	39.9 ± 91.1	43.2 ± 24.2	40.5 ± 51.4	42 ± 22.6	38.5 ± 5.6*	38.6 ± 62.6	31.9 ± 9.7*

RR, reverse remodeling; other abbreviations as in Table 1.
*$P < .05$ vs baseline.

Discussion

The findings of this study can be summarized as follows: 1) Echocardiographic volume−related response to CRT (ECHO++ and ECHO+) is associated with improvement in load-dependent parameters of LV diastolic function, a decrease in estimates of LV filling pressures, and reverse remodeling of the LA; and 2) patients with ECHO−/CLIN+ response exhibit a significant degree of improvement in diastolic function and LV filling pressures; in contrast, in patients with ECHO−/CLIN− response, no improvements in any of the parameters of LV diastolic function and LV filling pressure estimates were observed.

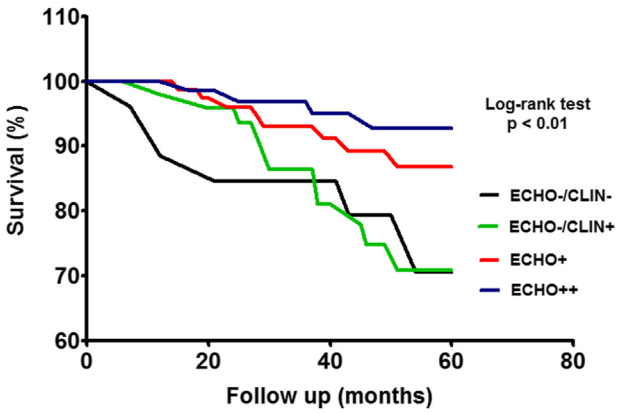

Fig. 2. Kaplan-Meier curves for cardiovascular mortality. Patients with slight or extensive left ventricular reverse remodeling had a more favorable outcome than patients with ECHO−/CLIN+ or ECHO−/CLIN− response. Although patients with ECHO−/CLIN+ response seem to have an initial benefit on survival compared with ECHO−/CLIN−, this difference does not persist at long-term follow-up. ECHO, echocardiographic response to cardiac resynchronization therapy (CRT); CLIN, clinical response to CRT.

Echocardiographic Response and Diastolic Function

In this study we have demonstrated an improvement in LV filling dynamics (decrease in E velocity and E/A ratio and increase in DT and filling time), a decrease in estimates of LV filling pressures (E/Em ratio and systolic PAP), and a secondary reverse remodeling of the LA in volume responders to CRT. Although a slight, albeit significant, improvement in DT was also observed in nonresponders, none of the other assessed parameters improved, and an increase in E/Em (potentially indicating elevated LV filling pressures) was demonstrated, in this latter group. These changes were observed together with changes in systolic function, suggesting that the improvement in diastolic function observed with CRT is linked to an improvement in LV systolic function.

Some previous studies have specifically analyzed the effect of CRT on the diastolic performance of the heart. In 50 CRT patients, Waggoner et al[2] observed an improvement in LV filling and a decrease in E/Em in echocardiographic responder patients. Similarly to our study, CRT responders did not show changes in Em or propagation velocity, suggesting a lack of CRT effect on LV relaxation properties. A similar study with a longer follow-up, conducted by Jansen et al,[3] observed a significant improvement in all the analyzed parameters (including Em and propagation velocity) in volume responder patients, whereas only an improvement in filling time was observed in nonresponders. Finally, in a recent study by Shanks et al,[15] a significant improvement in peak strain rate during the isovolumetric relaxation period (representative of LV relaxation) was demonstrated in volume responders. None of the conventional parameters assessed were significantly changed except for DT, which, similarly to our results, improved in both responders and nonresponders.

Our results confirm earlier findings and demonstrate that the improvement in diastolic function with CRT is coupled with an improvement of systolic function and, therefore, is seen mainly in echocardiographic responders.

Table 4. Extent of Response and Grade of Left Ventricular Diastolic Dysfunction

	Nonresponders (n = 28; 11.2%)		Clinical Responders (n = 56; 22.4%)		Slight RR (n = 84; 33.6%)		Extensive RR (n = 82; 32.8%)	
Grade of DD	Baseline	1 y	Baseline	1 y	Baseline	1 y	Baseline	1 y
Normal	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2)
Impaired relaxation	18 (64)	11 (39)	26 (46)	35 (62)	37 (44)	57 (68)	51 (62)	72 (88)
Pseudonormal filling	8 (28)	14 (50)	26 (46)	14 (25)	35 (41)	20 (24)	28 (34)	8 (108)
Restrictive	2 (7)	3 (10)	4 (7)	7 (12)	12 (14)	7 (83)	3 (47)	0 (0)

DD, diastolic dysfunction; RR, reverse remodeling.

Extent of Response: Clinical Response and Diastolic Function

Although clinical studies have mainly assessed response dichotomously (with the use of either clinical or echocardiographic parameters), not all patients respond equally to CRT in daily clinical routine. Whereas ventricular function almost normalizes in some patients, in others clinical parameters improve with only a modest effect, if any, on systolic function. To overcome the limitations of a dichotomous parameter of response, we divided our population into subgroups that take into account both clinical and echocardiographic parameters. This allowed assessment of the relationship between diastolic function, estimates of LV filling pressures, and clinical outcomes after CRT. The greater the response achieved with CRT, the more the parameters of LV diastolic function improved at follow-up, which further underscores the association between diastolic function and response to CRT. Similar results were observed regarding systolic PAP, which increases at follow-up in ECHO−/CLIN− patients, decreases significantly in ECHO++, and presents a nonsignificant improvement in the remaining intermediate subgroups. This finding may be relevant, taking into account the association between decrease in systolic PAP and better prognosis in CRT patients.[16]

Even more important, however, is the finding that patients exhibiting only a clinical response (ECHO−/CLIN+) had a small, but significant, improvement in diastolic function, in contrast to those patients without any kind of response. A slight trend of systolic PAP improvement at follow-up was also observed. This improvement in LV filling may explain why these patients obtain a clinical benefit of CRT, which translates to better functional class and quality of life, and indicates that this subgroup indeed obtains a benefit from the therapy that is not, as has been suggested,[13] the result only of a placebo effect. Why this subgroup present an improvement in PAP and diastolic function is not clear. Potentially, a slight improvement in systolic function (although not enough to cause a reduction in LV volumes and an increase in LVEF) could occur that would, in turn, improve load-dependent parameters and explain the clinical benefit of the therapy.

The relationship between clinical and echocardiographic responses to CRT has been investigated in earlier studies[9,12,13,17,18] demonstrating that ∼20%−25% of all patients present a positive clinical response but do not respond according to echocardiographic volumetric criteria. Our results suggest that an improvement in diastolic function could be responsible (at least partially) for the clinical improvement observed in this subgroup of patients (ECHO−/CLIN+).

Our findings suggest the existence or a spectrum—rather than an absolute presence of absence—of response, and this has implications regarding the definition of CRT response in daily practice. If clinical response without reverse remodeling (ECHO−/CLIN +) corresponds to a real effect of CRT, then these patients should be regarded as responders (at least to a lesser degree), and implantation of a CRT device in this population should not be considered to be useless.

Despite observing no significant impact on long-term survival, our study seems to suggest an early benefit on mortality in clinical-only responders, compared with nonresponders, that would be lost at longer-term follow-up. This initial better prognosis could justify the use of CRT as a bridge to heart transplantation or to a destination therapy in this subgroup of patients, although this finding warrants further evaluation in larger prospective studies. Finally, the question remains whether this small degree of response is associated with a reduction in other clinical events, such as hospital admissions, compared with nonclinical-nonechocardiographic responders. This question was not addressed in the present study and warrants further investigation.

Study Limitations

Although the sample size of the present study is relatively large, when dividing our population into subgroups of response the size of each subgroup is smaller and, as a consequence, the results should be taken with caution. We did not use strain rate parameters to more accurately assess the LV relaxation properties and therefore can not exclude a significant direct effect of CRT on LV relaxation. Additionally, no evaluation of right ventricular function was performed, which could be responsible for the clinical improvement observed in some patients of our population. Finally, the number of patients with grade 3 diastolic dysfunction (restrictive pattern) in our population was small (21 patients) and therefore no clear conclusions can be obtained regarding the effect of CRT on patients with severe diastolic dysfunction (grade 3). This issue warrants further investigation in new studies.

Conclusion

LV diastolic function improves with CRT. Patients with ECHO−/CLIN+ response show a significant improvement in LV diastolic function; no changes are observed in patients with ECHO−/CLIN− response. Our results suggest that clinical-only response (ECHO−/CLIN+) to CRT is secondary to a therapeutic effect, rather than a placebo effect, in most patients.

Disclosures

None.

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