Original articles

Effects of cardiac resynchronization therapy on disease progression in patients with congestive heart failure

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Cardiac remodeling; Heart failure; Pacing.

Background. **Cardiac resynchronization therapy (CRT) represents a new therapeutic modality of proven efficacy for selected patients with heart failure and ventricular asynchrony. The aim of this study was to assess the effects of CRT on clinical variables and cardiac remodeling in patients with moderate-to-severe congestive heart failure and inter/intraventricular conduction delays.**

Methods. **Thirty-seven patients (32 males, 5 females, mean age 73 ± 7 years), in NYHA functional class III-IV, with left ventricular ejection fraction (LVEF) ≤ 35%, QRS ≥ 150 ms, and left ventricular end-diastolic diameter (LVEDD) ≥ 55 mm, underwent CRT by biventricular pacing (InSync, InSync III, InSync ICD; Medtronic Inc.). Fourteen (37.8%) had a previous pacemaker, and 11 (29.7%) were in permanent atrial fibrillation. The QRS width, NYHA functional class, LVEDD, left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and LVEF were retrospectively evaluated in the period before CRT. For the purposes of the present study, the pre-CRT period was divided in two: T_{-2} (from 6 to 3 years) and T_{-1} (from 3 years to CRT). Moreover, these parameters were measured at the time of CRT (T_0) and prospectively in the post-CRT follow-up (T_p).**

Results. **Before CRT, a progressive worsening of the parameters was observed. The QRS duration steadily increased from T_{-2} to T_{-1} and T_0 (both p = 0.000). The NYHA functional class increased from T_{-2} to T_{-1} and T_0 (both p = 0.000). LVEDD and LVESD also increased and were higher at T_{-1} (p = 0.001 and p = 0.000, respectively) and at T_0 (both p = 0.000) compared to T_{-2}. Similar results were observed for LVEDV and LVESV. Finally, LVEF was higher at T_{-2} than T_{-1} and T_0 (both p = 0.000). After CRT, there was a reduction in the QRS duration and an improvement in the NYHA functional class compared to T_0 (both p = 0.000). LVEDD and LVESD were also reduced (p = 0.005 and p = 0.016, respectively), LVEDV and LVESV decreased (both p = 0.000), and LVEF increased (p = 0.000) with respect to T_0. A highly significant correlation was found between LVEDD and LVESD both in the pre- and post-CRT time intervals, with a non-significant difference between the two linear regression lines. Similar results were obtained for the correlations between LVEDV and LVESV.**

Conclusions. **Congestive heart failure is associated with a progressive widening of the QRS complex and a worsening of the clinical status and results in anatomic remodeling with deterioration of the left ventricular function. CRT induces opposite changes in QRS duration, clinical status, and left ventricular remodeling.**

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Introduction

Congestive heart failure is characterized by progressive left ventricular dilation and loss of contractile function, a condition referred to as "cardiac remodeling"[1]. The severity of left ventricular remodeling has been shown to carry an independent prognostic value[2]. Recently, it has been demonstrated that patients with congestive heart failure and electromechanical delay benefit from cardiac resynchronization therapy (CRT) with synchronous biventricular pacing. CRT improves the hemodynamic status in acute clinical conditions[3-5] and heart failure symptoms, exercise capacity, quality of life and systolic function chronically[6-8]; finally, a reduction in left ventricular diameters and volumes has also been demonstrated[9-13].

The aims of the present study were: 1) to demonstrate that heart failure progression is characterized by progressive left ventricular remodeling and an increased QRS duration; 2) to test the hypothesis that CRT is able to halt and possibly revert this process.

Methods

Study population. In the period from July 1999 to June 2002, 37 patients with moderate-to-severe congestive heart failure were consecutively treated with CRT. The etiology of heart failure was ischemic and non-ischemic heart disease. Patients with a pacemaker, implanted for conventional bradycardia indications, and those with permanent atrial fibrillation were not excluded.

CRT was considered in the presence of the following criteria: 1) NYHA functional class III or IV; 2) left ventricular end-diastolic diameter (LVEDD) ≥ 55 mm; 3) left ventricular ejection fraction (LVEF) ≤ 35%; and 4) QRS width ≥ 150 ms. At the time of CRT, patients were clinically stable for at least 1 month and were receiving optimized drug treatment for heart failure, including at least diuretics, ACE-inhibitors or the equivalent, and beta-blockers at the maximal tolerated dose. The last two classes of drugs were intentionally left unchanged until the first functional evaluation in order to define the role of CRT *per se*.

Demographics and clinical variables of the study population are reported in table I.

Implant procedure. Patients underwent implantation of a cardiac resynchronization device (InSync, models 8040, 8042; InSync ICD, model 7272; Medtronic Inc., Milan, Italy). The pacemaker implantation technique included a standard right atrial lead and a standard right ventricular lead (when not previously present); a specialized left ventricular lead (Attain models 2187, 4189, 4191, 4193; Medtronic Inc.) was placed into a lateral or postero-lateral cardiac vein through the coronary sinus[14]. In one patient, due to failure of transvenous placement, the left ventricular lead (Capsure Epi model 5071, Medtronic Inc.) was inserted in the left ventricular lateral free wall via an epicardial approach[15]. The pacing mode was DDD(R) with an atrioventricular delay optimized by Doppler echocardiography[16] or VVI(R) in patients with permanent atrial fibrillation.

Table I. Demographics and clinical variables.

Age (years)	73 ± 7
Sex (M/F)	32/5
IHD/non-IHD	19/18
Sinus rhythm/permanent AF	26/11
Previous pacemaker	14 (37.8%)
ACE-inhibitors	25 (67.6%)
Diuretics	36 (97.2%)
Beta-blockers	14 (37.8%)
Aldosterone antagonists	28 (75.7%)
Digoxin	28 (75.7%)

AF = atrial fibrillation; IHD = ischemic heart disease.

Study design. Patients successfully implanted with a CRT device underwent retrospective evaluation. The QRS width, NYHA functional class, LVEDD, left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV) and LVEF were retrieved from previous clinical files obtained during hospitalizations or outpatient visits for heart failure in the 6-year period prior to CRT. This pre-CRT period was divided in the time intervals from 6 to 3 years (T_{-2}) and from 3 years to CRT (T_{-1}). These parameters were also evaluated at the time of CRT (T_0) and during the post-implant period (T_p), with a prospective follow-up planned by the attending physician (Fig. 1).

Electrocardiographic and echocardiographic measurements. The QRS width was derived from the 12-lead electrocardiogram. After ventricular pacing, the QRS width was measured from the spike to the end of the QRS complex. All echocardiographic examinations were recorded and images were stored in the echocardiography laboratory (Hires Cardio - SHS Multimedia, version 1.0.124), as a routine practice since 1994. Echocardiographic measurements of the left ventricular size were obtained at M-mode echocardiography under two-dimensional guidance in the parasternal long-axis view, in accordance with the guidelines of the American Society of Echocardiography[17]. Biplane left ventricular volumes were calculated from the 4-chamber views, in accordance with the modified Simpson's rule[18]. The LVEF was calculated as follows: (LVEDV – LVESV)/LVEDV × 100.

Echocardiographic data were analyzed off-line by an independent observer blinded to the time-point being considered. Intraobserver variability for the measurement of left ventricular diameters and volumes were 1 and 3% respectively. All measurements were averaged from three cardiac cycles in patients with regu-

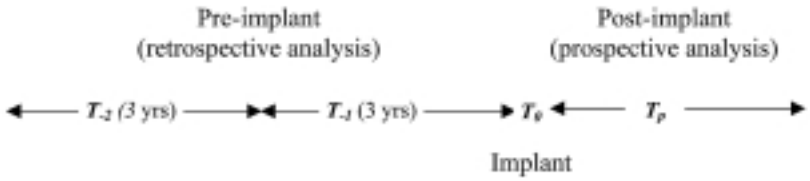

Figure 1. *Schematic representation of the different phases of the study. T_{-2} is the period lasting between 6 and 3 years before cardiac resynchronization therapy; T_{-1} is the 3-year period before cardiac resynchronization therapy; T_0 is the time of cardiac resynchronization therapy, and T_p is the post-cardiac resynchronization therapy period.*

lar rhythm and from five for those with irregular R-R intervals due to atrial fibrillation.

Statistical analysis. Continuous data are presented as mean ± SD. Differences between variables at time intervals were tested by using the general linear model for repeated measurements. The correlation between echocardiographic variables was evaluated using linear regression analysis. The η^2 statistic was used to describe the proportion of total variability attributable to CRT on the linear regression between left ventricular diameters and volumes. A p value ≤ 0.05 was considered as statistically significant.

Results

In the pre-CRT phase, the T_{-2} period was 51.8 ± 9.8 months with a mean of 3.2 ± 2.2 clinical files examined for each patient; the T_{-1} period was 14.2 ± 10.6 months and the number of clinical files analyzed was 4.0 ± 3.0 for each patient.

After CRT, a mean of 2.2 ± 1.4 files for each patient was obtained during a follow-up of 8.2 ± 7.7 months.

Parameter changes over time and effects of cardiac resynchronization therapy. Retrospective evaluation showed a significant progressive worsening of the evaluated parameters. The QRS width increased from 151.0 ± 24.2 ms at T_{-2} to 177.0 ± 23.0 ms at T_{-1} and 189.1 ± 35.4 ms at T_0 (both p = 0.000). The NYHA functional class worsened from 2.3 ± 0.5 at T_{-2} to 3.1 ± 0.5 at T_{-1} and 3.2 ± 0.5 at T_0 (both p = 0.000). LVEDD and LVESD progressively increased and were higher at T_{-1} (69.8 ± 6.0 mm, p = 0.001; and 56.7 ± 8.4 mm, p = 0.000, respectively) and T_0 (69.8 ± 8.0 and 56.7 ± 7.2 mm, respectively; both p = 0.000) than at T_{-2} (64.4 ± 8.0 and 49.9 ± 7.8 mm, respectively). A similar trend was observed for LVEDV and LVESV from T_{-2} (184.5 ± 44.6 and 122.4 ± 40.9 ml, respectively) to T_{-1} (216.7 ± 70.0 ml, p = 0.001; and 151.6 ± 50.0 ml, p = 0.000, respectively) and T_0 (235.8 ± 64.2 and 176.0 ± 54.9 ml, respectively; both p = 0.000). Finally, LVEF was higher at T_{-2} (38.8 ± 8.3%) than at T_{-1} and T_0 (29.9 ± 5.3 and 27.4 ± 6.0%, respectively; both p = 0.000) (Fig. 2).

CRT induced a dramatic change in all parameters. A reduction in the QRS width (162.1 ± 13.3 ms, p = 0.000) along with an improvement in NYHA functional class (2.1 ± 0.2, p = 0.000) was observed from T_0. LVEDD and LVESD increased from T_0 (66.1 ± 5.8 mm, p = 0.005; and 53.6 ± 8.0 mm, p = 0.016, respectively). LVEDV (175.3 ± 60.1 ml) and LVESV (117.8 ± 46.6 ml) were also smaller than at T_0 (both p = 0.000); and the LVEF increased to 32.8 ± 4.7% (p = 0.000) with respect to T_0 (Fig. 2).

These changes were observed in all patients, regardless of the etiology of cardiomyopathy, permanent atrial fibrillation, and previous conventional pacemaker.

Correlation between pre- and post-cardiac resynchronization therapy left ventricular diameters and volumes. A highly significant correlation was found between 1) LVEDD and LVESD, and 2) LVEDV and LVESV both in the pre- and post-CRT time intervals; linear regression analyses were not influenced by CRT (η^2 = 0.003, p = 0.550; and η^2 = 0.009, p = 0.189, respectively) (Fig. 3).

Discussion

Our study shows that progression of congestive heart failure is characterized by remodeling and deterioration of the left ventricular systolic function. This process is reversed by CRT, which improves systolic function, decreases left ventricular volumes and reduces symptoms. In our patients, these changes were achieved regardless of medical therapy with ACE-inhibitors or the equivalent and beta-blockers. Contrary to previous studies[9,10], in the early post-implant period, medical therapy was intentionally maintained unmodified so that the confounding effect of increased medical therapy (particularly beta-blockers) was avoided.

It is important to note that our patient population represents the "real word" of heart failure, with a mean age almost 10 years higher compared to that reported in the available randomized trials[6-8]. This aspect may explain the relatively low percentage of patients on beta-blocker therapy in our population and is consistent with previous data showing a lower utilization of beta-blockers in the elderly[19].

ACE-inhibitors, beta-adrenergic blocking agents and antialdosterone therapy are associated with a significant reduction in morbidity and mortality in congestive heart failure[20,21]; moreover, ACE-inhibitors and beta-blockers have been shown to slow down, and in some cases even reverse, cardiac remodeling[21-23]. In previous studies performed on patients with congestive heart failure and ventricular asynchrony, CRT on top of optimized medical therapy was able to improve the echocardiographic parameters of left ventricular remodeling[9-12]. Recently, a large study confirmed that CRT caused significant reverse remodeling and that the outcome was related to the degree of echocardiographic improvement[13]. Our study is unique in that we performed a long retrospective analysis, showing evidence of an association between clinical progression of heart failure and cardiac remodeling. This progression was not only halted but even reversed by CRT within a short time. Moreover, CRT appeared to be equally effective regardless of permanent atrial fibrillation, previous conventional pacemaker implantation or ischemic etiology of congestive heart failure. The latter finding is not in agreement with previous works suggesting that the benefit of CRT may be less in ischemic cardiomyopathy[13]. It is likely that the limited number of patients

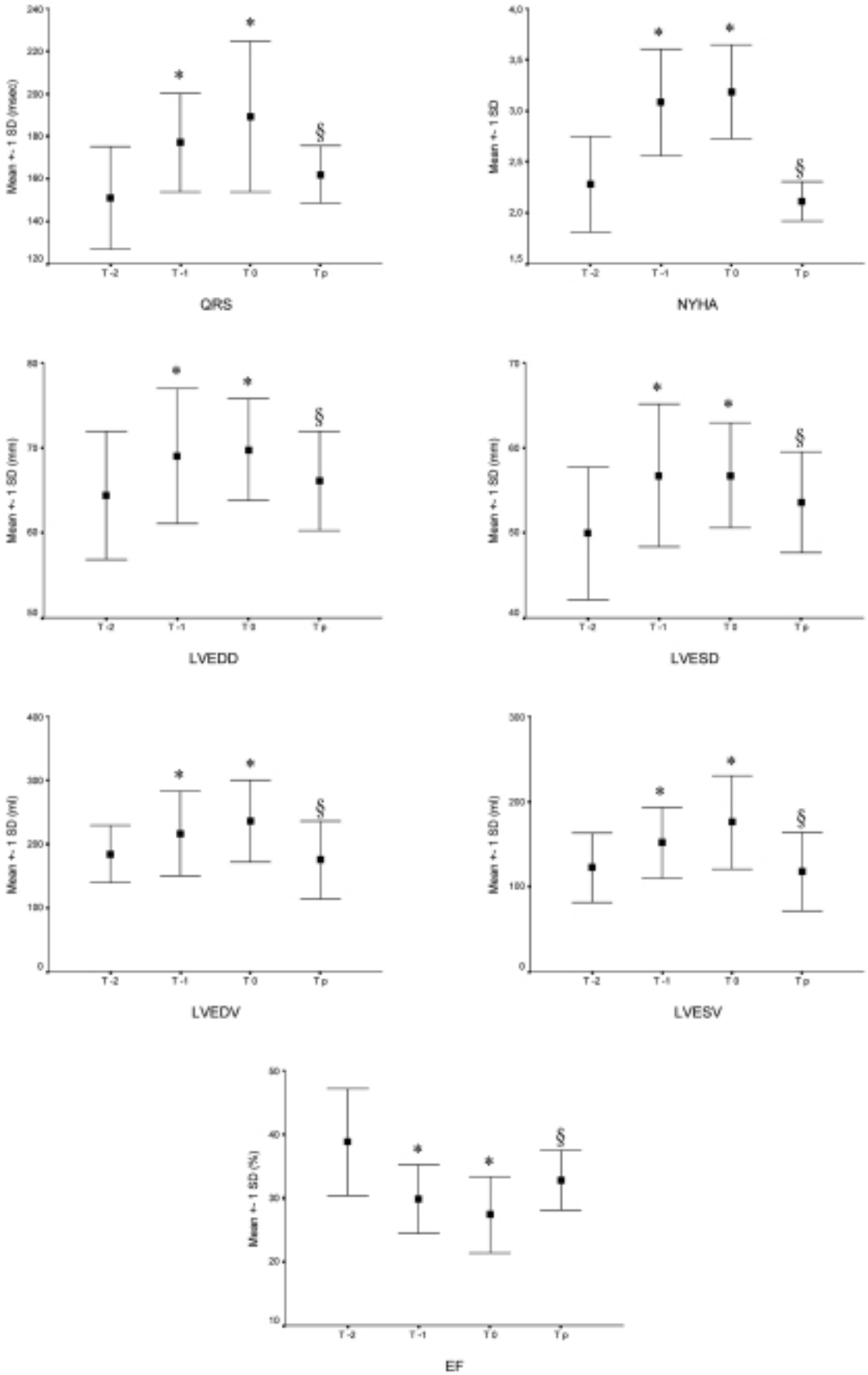

Figure 2. *Changes in the QRS width, NYHA functional class, left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV) and left ventricular ejection fraction (EF) before (time T_{-2} and T_{-1}) and after (time T_p) cardiac resynchronization therapy (time T_0). * significant difference vs time T_{-2}; § significant difference vs time T_0.*

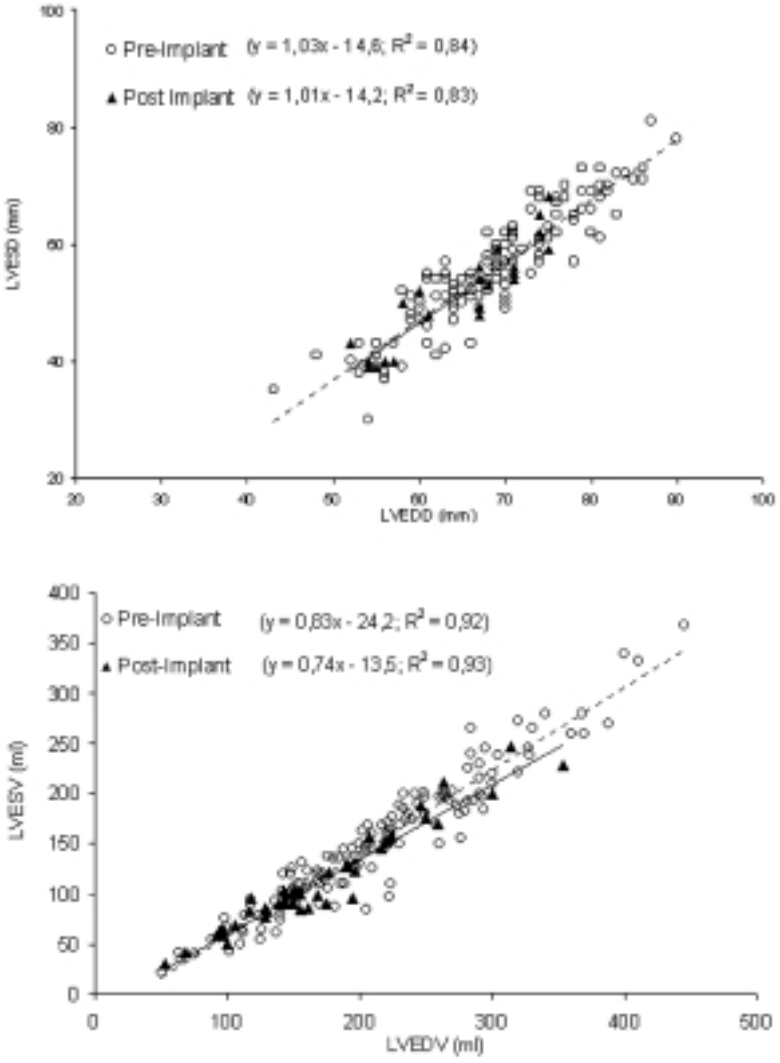

Figure 3. *Correlation between left ventricular diameters and volumes before and after cardiac resynchronization therapy. LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume.*

included in our series prevented us from appreciating this difference.

Progressive QRS widening frequently develops in patients with cardiomyopathy during the course of the disease[24]. It is known that the magnitude of inter- and intraventricular asynchrony is proportional to QRS duration, and that the presence of left bundle branch block determines a decrease in contraction performance and an abnormal diastolic filling pattern[25,26]. The effects of left bundle branch block on systolic and diastolic left ventricular function may in turn induce or exacerbate the remodeling process[26,27]. Thus, a vicious cycle of progressive QRS widening and left ventricular dysfunction ensues. This pattern was evident in our pre-implant echocardiographic data. The ability of CRT to induce reverse remodeling may be attributed to enhancement of the synchrony of contraction of the left ventricle and between left and right ventricular systole[28]. These effects are associated with a significant reduction in left ventricular diameters and volumes[9,11-13]. However, the modality of such a reduction after CRT has not yet been investigated. We observed that the regression line depicting the correlation between LVESD and LVEDD (as well as volumes) in the pre-CRT period showed an almost identical slope to that obtained after CRT. This finding suggests, but does not prove, that at least to some extent CRT actually acts as a true reverse gear in the natural history of the remodeling process.

Study limitations. The first phase of the study was retrospective. The data presented were collected in a relatively small patient population, recruited over a long time span and treated on the basis of conventional heart failure therapy at the time of enrolment. The number of observations for any time interval is not homogeneous and data on concomitant mitral regurgitation and the potential beneficial effects of CRT on this aspect were not reported. Since patients undergoing CRT were

closely monitored and followed after implantation, it cannot be excluded that, as observed for other treatments[29], a more thorough medical control was *per se* able to induce a significant clinical improvement. However, data on left ventricular remodeling suggest that this mechanism, although present, is not sufficient to explain the whole benefit observed with CRT.

In conclusion, the data presented demonstrate that disease progression of congestive heart failure is associated with left ventricular remodeling and that CRT is effective in improving symptoms and reducing left ventricular diameters and volumes. This mechanism can be referred to a reverse remodeling. The reduction in NYHA functional class and the improvement in systolic function become evident in the early follow-up period and are maintained at 1 year. By this time, patients are reverted to the status they had 6 years prior to CRT.

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