Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 55, No. 17, 2010
ISSN 0735-1097/10/$36.00
doi:10.1016/j.jacc.2010.01.022

QUARTERLY FOCUS ISSUE: HEART FAILURE

Long-Term Reverse Remodeling With Cardiac Resynchronization Therapy

Results of Extended Echocardiographic Follow-Up

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Objectives The purpose of this study was to describe the long-term course of left ventricular remodeling induced by cardiac resynchronization therapy (CRT), adjusting for the confounding effect of patient loss due to disease.

Background Reverse remodeling has been identified as the primary mechanism of improved symptoms and outcome in heart failure patients.

Methods A total of 313 consecutive patients who underwent CRT with available baseline echocardiograms and subsequent clinical and echocardiographic follow-up were included in the analysis. Long-term follow-up included all-cause mortality, heart transplantation, and implantation of a left ventricular assist device. Longitudinal data analysis of left ventricular end-systolic volume index (LVESVi) was performed to adjust for the confounding effect of patient loss during follow-up.

Results Patients with uneventful survival had a lower baseline LVESVi (Δ = 8.6 ml/m^2, SE = 4.6 ml/m^2, $p < 0.0001$) and a decreased LVESVi by −0.11 ml/m^2/day during first 6 months, whereas the LVESVi remained unchanged in patients with adverse events ($p < 0.0001$). Beyond 6 months, the LVESVi remained unchanged in patients with uneventful survival, whereas the LVESVi continued to increase in those with adverse events at a rate of 0.01 ml/m^2/day ($p < 0.0001$). Predictors of reverse remodeling were nonischemic etiology, female sex, and a wider QRS duration ($p < 0.0001$, $p = 0.014$, and $p = 0.001$, respectively). In the majority of patients, 6 months indicates a break point after which reverse remodeling becomes significantly less pronounced.

Conclusions CRT patients with uneventful survival show a significant decrease in the LVSVi at 6 months and generally maintain this response in the long term. Those with adverse outcomes are characterized by left ventricular dilation despite CRT. (J Am Coll Cardiol 2010;55:1788–95) © 2010 by the American College of Cardiology Foundation

The beneficial effect of cardiac resynchronization therapy (CRT) for symptomatic patients with systolic heart failure and wide QRS complex has been shown in several clinical trials (1–6). Evidence suggests that the improved outcomes observed with CRT are associated with reverse remodeling, a process characterized by a reduction in left ventricular (LV) volumes leading to improved systolic and diastolic function (7). The structural and functional changes associated with this process occur as early as 3 months and are even more pronounced by 6 months, a time interval by which the magnitude of reverse remodeling has been shown to predict the long-term prognosis in these patients (8–11). Although the MIRACLE (Multicenter InSync Randomised Clinical Evaluation) study showed that these beneficial changes are generally sustained at 12 months, this study also demonstrated that LV volumes may increase at 1-year follow-up, particularly in the ischemic population (9). To our knowledge, no other studies have evaluated the temporal course of LV reverse remodeling at a more extended follow-up. One of the problems arising with this type of analysis is that the evaluation of long-term response to CRT is inherently confounded by the loss of patients during the follow-up period, most likely attributable to those with the development of minimal or no reverse remodeling.

The main purpose of the present study was to overcome this limitation and investigate serial changes in LV size and

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Manuscript received June 8, 2009; revised manuscript received November 20, 2009; accepted January 5, 2010.

function by using longitudinal data analysis in a consecutive cohort of patients with long-term follow-up. We also sought to identify the clinical determinants of these time-dependent changes, including potential modifiers of LV remodeling after the first 6 months of CRT. Our final objective was to relate the course of LV remodeling with long-term outcome in CRT patients.

Methods

Study population and study design. The records of all heart failure patients who underwent CRT device implantation at the Cleveland Clinic between January 2003 and June 2006 were reviewed for this study. The criteria applied for CRT in our institution include recent New York Heart Association (NYHA) functional class III/IV symptoms despite optimal medical therapy, QRS width ≥120 ms, and LV ejection fraction ≤35%. From this population, we included patients who had longitudinal follow-up at our institution. Patients were excluded if no baseline transthoracic echocardiographic study was performed at the Cleveland Clinic before implantation. The minimal echocardiographic follow-up required for inclusion was set at 90 days after the procedure; patients with a major event during these first 3 months (early death or urgent transplantation) were excluded. Patients with a device implanted before 2003 undergoing exchange of their battery during the specified period for any reason (end of life or previous removal of a device due to endocarditis) were also excluded.

The etiology of heart failure was considered ischemic on the basis of a clinical history of myocardial infarction (with electrocardiographic evidence of infarct location) or a history of revascularization. In a subset of patients with ischemic cardiomyopathy who underwent myocardial viability testing by single-photon emission computed tomography or positron emission tomography with fluorodeoxyglucose before CRT, scar burden was quantified as a percentage of the total myocardium using the 17-segment polar map (12). LV lead position was assessed by reviewing lateral chest radiographs obtained after implantation, categorizing the LV lead position as anterior, lateral, or posterior (13).

The primary end point was a composite of death from any cause (determined with the Social Security Death Index), need of heart transplantation, and support with a left ventricular assist device (LVAD). The study protocol was approved by the Cleveland Clinic Institutional Review Board.

Device implantation and programming. Patients considered at risk of sudden cardiac death received CRT including an implantable cardioverter-defibrillator. Transvenous lead positioning was guided by venography with a preference for a lateral or posterolateral vein as an implantation site. In case of failure of or technical difficulties with the transvenous approach, an epicardial steroid-eluting passive lead was implanted through a limited thoracotomy. The atrioventricular delay was routinely optimized before discharge with the assistance of a device programmer and a cardiac sonographer, targeting stage I diastolic filling by Doppler mitral inflow (14).

Abbreviations and Acronyms

CRT = cardiac resynchronization therapy
LV = left ventricular
LVAD = left ventricular assist device
LVESVi = left ventricular end-systolic volume index
NYHA = New York Heart Association

Echocardiographic analysis. Baseline and every subsequent echocardiogram obtained at our institution during the follow-up of the patient after initiation CRT were systematically reviewed and measured by 2 experienced readers. The 2- and 4-chamber images were used to calculate left ventricular end-diastolic volume, left ventricular end-systolic volume, and left ventricular ejection fraction using Simpson's biplane method (15). Volumes were indexed according to body surface area. The interobserver variability and intraobserver variability for volume analysis were determined from 49 random studies.

The severity of mitral regurgitation was measured from the apical 4-chamber view. The left atrial and mitral regurgitant jet areas were measured by planimetry, allowing calculation of the ratio of jet/left atrial area (16). Mitral regurgitation severity was graded as 0 (none), 1+ (jet/left atrial area <10%), 2+ (jet/left atrial area 10% to 20%), 3+ (jet/left atrial area 20% to 45%), and 4+ (jet/left atrial area >45%). LV mechanical dyssynchrony was not consistently assessed in all patients before CRT.

Statistical methods. Detailed statistical methods are available (Online Appendix). Briefly, to assess the evolution of left ventricular end-systolic volume index (LVESVi) during CRT, we applied a linear mixed effects model with unstructured covariance for random effects (SPSS Inc., Chicago, Illinois) (17). In a first step, we assessed the impact of CRT on LVESVi. On the basis of the MIRACLE data (9), the estimated LVESVi curve with CRT was assumed to flatten out after showing an initial decrease. Piecewise linear regression was used to model the effect of time for both fixed and random effects, with potential break points of 90, 180, 360, and 720 days being tested. Minimal likelihood ratio was used to select optimal break point. In a second step, we assessed whether the group of patients with an adverse event (death, heart transplantation, or LVAD implantation) had a different LVESVi evolution after CRT. In a third step, we tested the impact of potential prognostic variables selected by survival analysis.

To assess prognostic variables, we performed a stepwise Cox proportional hazards regression with the combined end point of death, heart transplantation, and LVAD implantation. Variables assessed as potential predictors included age, sex, NYHA functional class, QRS duration, heart failure etiology, and baseline LVESVi.

To assess determinants of late (>180 days) changes in LVESVi, in a total of 197 patients with at least 2 additional studies obtained >180 days after the start of CRT, we

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calculated the slopes of the individual LVESVi/time relationships, with only the data obtained after 180 days for this analysis. We subsequently used forward stepwise multiple linear regression to assess possible predictors (i.e., age, sex, QRS duration, initial LVESVi, heart failure etiology) of the slopes of the individual LVESVi/time relationships.

The interobserver variability and intraobserver variability were expressed as the SD of the difference between 2 paired measurements and as a percentage of variability (SD divided by the average value).

Standard variables in the text are reported as mean ± SD, unless otherwise specified, and as 95% confidence intervals in the figures. The slopes of regression lines obtained by longitudinal data analysis are presented along with the corresponding SE of the estimate. A p value of <0.05 was taken to represent significance, except for third-order interactions, where p value of <0.2 was taken to represent significance.

Results

Patients. Of the 1,067 consecutive patients undergoing CRT device implantation between January 2003 and June 2006 at the Cleveland Clinic, 337 (31.5%) met the prespecified inclusion criteria. An additional 24 patients were excluded due to poor image quality, resulting in a cohort of 313 patients. The baseline characteristics of our study patients and of the excluded population are described in Table 1. Although a major event within the first 90 days after implantation was one of the exclusion criteria, survival at 1-, 2-, and 3-year follow-up was eventually fairly similar for study patients compared with excluded patients (94%, 83%, and 72% vs. 86%, 78%, and 73%, respectively; p = 0.46 by log-rank statistics).

During a follow-up of 1,301 ± 573 days (range 111 to 2,192 days), 118 (37.6%) study patients reached the end point (n = 102, n = 12, and n = 4 for death, heart transplantation, and LVAD implantation, respectively).

Twenty-nine study patients received CRT despite being in NYHA functional class II just before pacemaker implantation, according to the clinicians' discretion. Also, in 12 patients, CRT was started, although the electrocardiogram immediately before implantation showed a QRS complex duration of <120 ms because of either intermittent left bundle branch block (n = 3), requirement of pacemaker implantation while having heart failure and an ejection fraction <35%, or in 5 patients because of significant intraventricular dyssynchrony (assessed by echocardiography at the specific request of the heart failure physician to determine whether they might benefit from CRT) (18,19).

Estimated LVESVi curve for the whole study cohort. Figure 1 shows the observed values of the LVESVi during CRT superimposed with the fitted line obtained by piecewise regression. The optimal break point for the piecewise regression was found to be at 180 days. Using this break point, both the initial slope of the change in the LVESVi and the subsequent change in this initial slope after 6 months were highly significant ($p < 0.0001$ for all). In addition, the absolute values of the initial slope of the LVESVi changes and the subsequent change in the initial slope over time were similar (0.063 ± 0.008 ml/m^2/day and −0.061 ± 0.008 ml/m^2/day, p = 0.86 by the Wald test), indicating that piecewise linear regression with 2 independent slopes could be substituted by piecewise linear regression with the second slope parallel to the x axis (see section on statistical methods). In other words, after an initial decrease in the LVESVi, a break point is reached at 6 months, after which the course of the LVESVi for the entire study cohort remained unchanged. The mean decrease in the LVESVi observed during the first 12 months after CRT was 13.1 ± 26%.

Estimated LVESVi curves for patients with and without adverse events. Next, we compared the changes in the LVESVi in patients with survival with patients who died or underwent heart transplantation or LVAD implantation. Patients who reached the combined end point had a significantly larger initial LVESVi (by 18.6 ml/m^2, SE = 4.6 ml/m^2, $p < 0.0001$) (Fig. 2). Importantly, during the initial 6 months, patients with an uneventful survival demonstrated a decrease in the LVESVi by −0.11 ml/m^2/day, whereas the LVESVi was slightly increased in patients with adverse events ($p < 0.0001$ for the difference in initial slopes). Similarly, after 6 months, survivors showed stable

Table 1 Baseline Characteristics of the Study Cohort and Excluded Patients

	Study Cohort (n = 313)	Excluded Patients (n = 754)
Male sex (%)	69	73
Ischemic etiology (%)	52	60*
Age (yrs)	64.6 ± 11.8	67.7 ± 11.8†
NYHA functional class II/III/IV (%)	8/83/9	10/72/8
LVEF (%)	26 ± 10	24 ± 10‡
LVESVi (ml/m^2)	93 ± 40	86 ± 40‡
MR severity: 0/1+/2+/3+/4+	93/94/78/35/13	156/263/179/120/36
Previous mitral valve surgery (repair/replacement)	18/5	78/12
Sinus rhythm (%)	81	78
QRS width (ms)	162 ± 29	159 ± 31
LBBB or continuous RV pacing (%)	72	76
Scar burden (%)§	34.4 ± 19.5	33.3 ± 17.0
ICD (%)	93	89
ACEI/ARB (%)	86	84
Beta-blockers (%)	85	83
Posterior/lateral/anterior lead position (%)	67.0/28.6/4.4	59.0/36.1/4.9

Continuous variables are given as mean ± SD and categorical variables as percentage. *$p < 0.05$. †$p < 0.001$. ‡$p < 0.01$. §Based on positron emission tomography/single-photon emission computed tomography viability studies performed in a subgroup of 131 patients with ischemic cardiomyopathy.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; LVESVi = left ventricular end-systolic volume index at baseline; MR = mitral regurgitation; NYHA = New York Heart Association; RV = right ventricle.

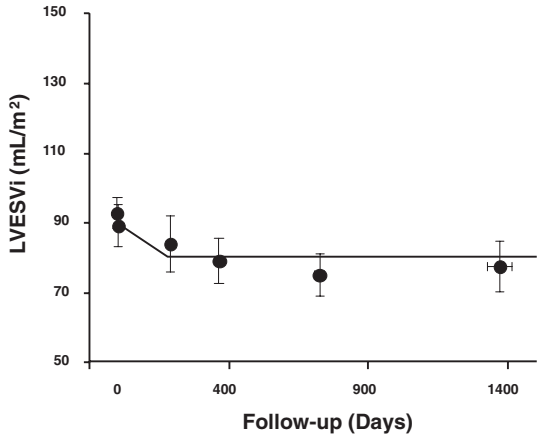

Figure 1 **Estimated Course of LVESVi for the Entire Study Cohort (n = 313)**

Markers represent the average of the observed data obtained before implantation (time zero) over the intervals of 1 to 30 days, 120 to 249 days, 250 to 499 days, 500 to 999 days, and ≥1,000 days. **Error bars** represent 95% confidence intervals. Piecewise regression line is obtained by mixed model approach (see statistical methods for details). After a decrease during the initial 6 months, the regression line becomes flat ($p > 0.1$ for the slope of regression line compared with 0°). LVESVi = left ventricular end-systolic volume index.

volumes, whereas the LVESVi continued to increase in nonsurvivors at an average rate of 0.01 ml/m^2/day ($p < 0.0001$ for the difference in the late slopes).

Survival analysis. Because the final outcome cannot be used as a predictor of the change in the LVESVi, a Cox model was used to identify survival predictors and to determine whether these could serve as predictors of LVESVi changes after CRT. Table 2 shows 5 significant multivariable predictors of outcome. Baseline mitral regurgitation severity did not predict an adverse outcome ($p = 0.13$).

Although LV lead position was not included in the analysis because this information was available for only 255 (82%) of our patients, a small impact of lead position on outcome was observed in a univariable Cox model ($p = 0.04$ for the difference between posterior, lateral, and anterior locations). Additionally, in 131 ischemic patients who had an imaging evaluation of myocardial scarring, scar burden also was found to be a significant predictor of outcome ($p = 0.003$).

Predictors of the course of LV remodeling. We then dichotomized the continuous predictors of outcome as described in the statistical methods section. Although NYHA class was the strongest predictor, it was not possible to dichotomize this variable in an adequate manner because most of the patients were in NYHA functional class III (Table 2). Despite being a strong predictor of survival, the baseline LVESVi did not influence the change in the LVESVi during follow-up.

Figures 3A and 3B show the impact of heart failure etiology and sex on LVESVi changes during follow-up. Male patients and patients with ischemic etiology had a significantly smaller decrease in the LVESVi during the initial 6 months ($p < 0.0001$ and $p = 0.014$ for the difference in initial slopes, respectively). Furthermore, during the initial 6 months, female nonischemic patients experienced a larger LVESVi decrease (i.e., more reverse remodeling) than other groups of patients ($p = 0.06$ for interaction in the difference in initial slopes).

Figure 4 shows the impact of QRS duration on LVESVi changes during follow-up. Patients with a QRS duration <140 ms had significantly less LVESVi decrease during the first 6 months ($p = 0.001$ for the difference in initial slopes). No interaction was detected between QRS duration and either sex or heart failure etiology. Furthermore, ischemic patients with scarring involving >32.5% of the total myocardium also had a significantly smaller decrease in the LVESVi during the first 6 months after CRT ($p = 0.005$ for the difference in initial slopes).

Late changes in LVESVi. We assessed determinants of LV remodeling after the initial 6 months of follow-up in 197 patients with data available to calculate late changes in the LVESVi. The slope of the average change in the LVESVi after 6 months was 0.0078 ± 0.054 ml/m^2/day (p = NS vs. 0), indicating that, on average, the LVESVi

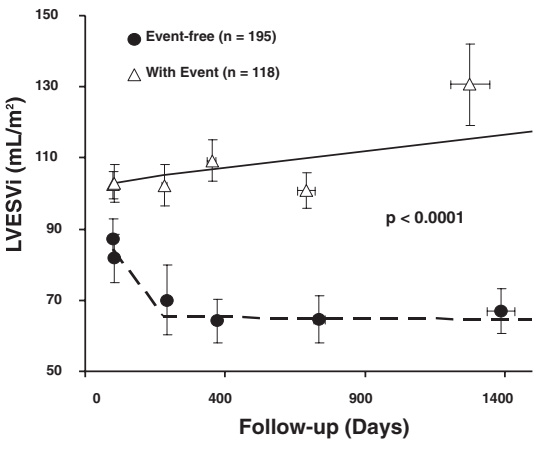

Figure 2 **Estimated Course of LVESVi for Patients With an Event-Free Survival Versus Patients With Adverse Events (Death, Heart Transplantation, or the Need for an LVAD)**

Graph is drawn as in Figure 1. Patients with event-free survival show a large initial LVESVi decrease, with the regression line becoming flat afterward. In contrast, patients with adverse events show a small LVESVi increase during the first 6 months, continuing approximately at the same rate throughout the rest of follow-up ($p < 0.0001$ for the difference in the course of the LVESVi during both the initial 6 months and during late follow-up). LVAD = left ventricular assist device; LVESVi = left ventricular end-systolic volume index.

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Table 2 Multivariable Cox Proportional Regression Analysis Showing Significant Predictors of Outcome (Death, Heart Transplant, or Left Ventricular Assist Device Implantation) in Cardiac Resynchronization Therapy Patients

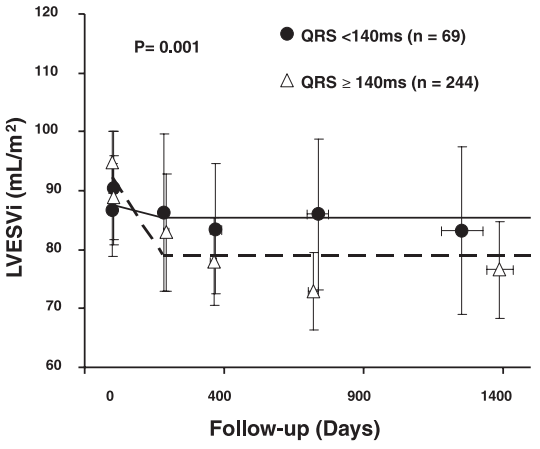
	Beta	SE	Wald	p Value
NYHA functional class >III	0.873	0.258	11.44651	0.0007
LVESVi (ml/m^2)	0.007	0.002	10.59364	0.0011
Ischemic etiology	0.656	0.208	9.912443	0.0016
Male sex	0.714	0.268	7.097843	0.0077
QRS duration (ms)	−0.009	0.003	6.937096	0.0084

Variables are presented in order of strength of relationship. The presence of higher functional class, larger end-systolic volume, ischemic etiology, male sex, and shorter QRS duration predicted worse outcome of patients undergoing resynchronization therapy.

Abbreviations as in Table 1.

remained stable after 180 days. In a univariable analysis, only the initial LVESVi (r = 0.15, p = 0.04) showed a weak positive correlation with a late increase in the LVESVi, suggesting that late recurrent dilation tended to develop in patients with a larger initial LVESVi, whereas the opposite was true for patients with a smaller initial LVESVi (Fig. 5).

Interobserver and intraobserver variability. For LV end-systolic volume, the intraobserver variability and interobserver variability were 8 ± 8 ml (5 ± 5%) and 16 ± 12 ml (10 ± 8%), respectively.



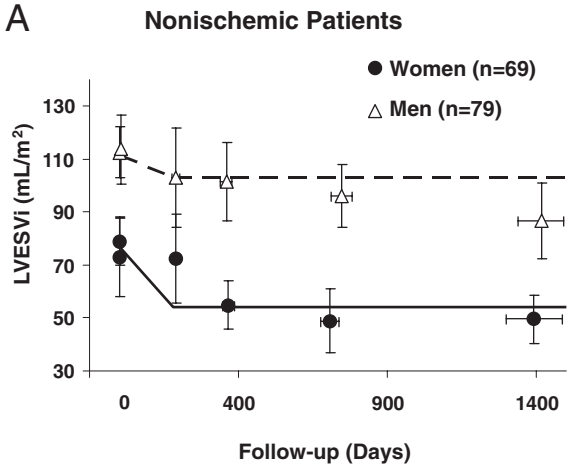
Follow-up (days):	pre	1-30	120-249	250-499	500-999	≥1000
QRS <140ms	69	43	42	42	40	26
QRS ≥ 140ms	244	147	88	140	197	163

Figure 4 Estimated Course of LVESVi for Patients Stratified According to QRS Duration

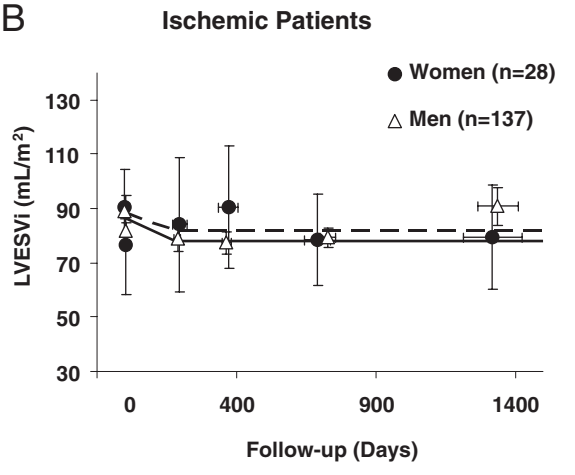
Graph is drawn as in Figure 1. A significant difference in the initial left ventricular end-systolic volume index (LVESVi) decrease was observed with a cutoff value of 140 ms (p = 0.001 for the difference in initial slopes of LVESVi change).

Discussion

The main findings of our study, which focused on the long-term course of LV remodeling after CRT, are as follows. At 6 months, a break point was observed after which additional changes in the LVESVi became much less pronounced. Female sex and a nonischemic etiology of heart failure were associated with a much greater initial response



Follow-up (d):	pre	1-30	120-249	250-499	500-999	≥1000
Men	79	56	34	50	60	52
Women	69	38	32	47	65	49



Follow-up (d):	pre	1-30	120-249	250-499	500-999	≥1000
Men	137	84	55	71	88	63
Women	28	12	9	14	24	25

Figure 3 Estimated Course of LVESVi for Patients With and Without Ischemic Heart Disease as the Cause of Heart Failure

Estimated course of left ventricular end-systolic volume index (LVESVi) for patients with **(A)** and without **(B)** ischemic heart disease as the cause of heart failure. Patients are stratified according to sex. Graphs are drawn as in Figure 1. Female sex and nonischemic etiology were associated with a larger LVESVi decrease during the first 6 months (p = 0.0001 and p = 0.014, respectively, for the difference in initial slopes of LVESVi change). This decrease was even more prominent in female nonischemic patients (p = 0.06 for interaction in initial slopes of LVESVi change; for details, see statistical methods). p < 0.0001 women versus men; p = 0.014 nonischemic versus ischemic; p = 0.06 for gender × etiology interaction.

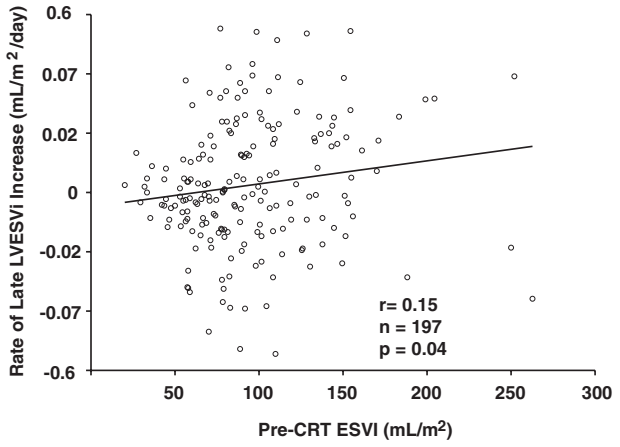


Figure 5 **Correlation Between Late Changes in the LVESVi (Changes Occurring After the Initial 180 Days After CRT) and Baseline LVESVi**

Correlation between late changes in the left ventricular end-systolic volume index (LVESVi) (changes occurring after the initial 180 days after cardiac resynchronization therapy [CRT]) and baseline LVESVi.

to CRT. Equally, patients with a baseline QRS duration >140 ms or ischemic patients with a smaller scar burden experienced a greater initial decrease in the LVESVi. Although, on average, the LVESVi seemed to be constant at late follow-up, a weak trend for the development of late recurrent dilation was seen in patients with initially large ventricles and vice versa.

CRT and long-term remodeling. Despite the survival benefit of CRT for patients with advanced heart failure, the cumulative mortality is still high in this group of patients, ranging from 15% to 18% at 1 to 2 years in randomized, controlled trials to 34% or higher at 5-year follow-up, as found by some observational studies (3,5,20). The substantial loss of patients creates a challenge when presenting long-term follow-up data on LV remodeling because the extent of reverse remodeling has been shown to be correlated with long-term prognosis in CRT patients (10,11). Paradoxically, this may lead to the false conclusion that LV volumes continue to decrease with CRT even after more than 2 years, whereas, in fact, only patients with a better response are represented in these data.

Another problem with observational studies is that the timing interval between (clinically indicated) studies is often variable, which complicates comparison of serial LV volume changes between patients during long-term follow-up. In the present study, we addressed these methodological difficulties by applying a linear mixed effects model that allowed us to analyze long-term changes in cardiac structure and function with CRT in a truly longitudinal fashion, leading to results that are still robust in the setting of sampling variability and inherent patient dropout due to disease. This approach further extends our knowledge of the course of LV remodeling, which until now was mostly limited to 12 to 18 months of follow-up (9,21).

The first important finding in our analysis is that the LVESVi curve for the whole study population shows an abrupt decrease immediately after initiation of CRT and that this decrease continues until 6 months after implantation. At 6 months, a clear break point was observed, with the LVESVi remaining relatively unchanged throughout the rest of follow-up. Patients with an uneventful survival showed a similar pattern of response with a more pronounced decrease in the LVESVi during the first 6 months. In contrast, patients with adverse events demonstrated a markedly different course of LV remodeling with the LVESVi remaining initially unchanged at best and subsequently showing a steady increase despite CRT. These findings add evidence to the concept that the process of reverse remodeling itself is directly associated with prognosis of CRT, even in mildly symptomatic patients (22). The clinical implication of our results is that they provide a clear rationale for performing echocardiography at 6 months of CRT as means of risk stratification and as a method to predict the future course of LV remodeling. Based on these results, patients who do not show a decrease in the LVESVi at 6 months are unlikely to do so thereafter, a finding that has a significant impact on subsequent management of these patients. We have shown that the rate of adverse events in this population may be lowered by referring these patients to a multidisciplinary CRT optimization clinic to uncover reversible causes of a suboptimal response to CRT (e.g., rhythm abnormalities, suboptimal lead positioning, device programming, suboptimal indications for CRT) (23). Our results indicate that the 6-month time point may be the optimal time to refer selected patients for an evaluation of nonresponse as a step in their further clinical management.

Determinants of CRT-induced remodeling. Another important goal of this study was to identify clinical determinants of these time-dependent changes in LV size and function secondary to CRT. Because outcome was significantly associated with a change in the LVESVi after CRT, many variables associated with long-term outcome in our population were also found to have a direct effect on the time course of LV remodeling.

Similar to previous findings, patients with ischemic heart disease demonstrated less improvement in LV function during the first 6 months (8,9). However, whereas the MIRACLE study found that the beneficial decrease in LV volumes seen at 6 months had partially regressed by 12 months in the ischemic population, our longer term follow-up indicates that there is no precise point in time where the initial benefit of CRT is eventually offset by recurrent late LV dilation, which could have reflected the natural history of ischemic cardiomyopathy. Our findings also help to explain why the beneficial effects of CRT on symptoms, quality of life, morbidity, and mortality are still preserved in the ischemic population at long-term follow-up, as shown previously (5,21).

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Furthermore, although heart failure patients should not be denied CRT on the basis of an ischemic etiology alone, our data also suggest that it may be wise to consider scar burden before offering CRT in this subgroup of patients. In those patients who underwent viability testing by positron emission tomography with fluorodeoxyglucose or single-photon emission computed tomography before device implantation, more extensive LV scarring was clearly associated with less favorable late remodeling and a worse outcome. Large prospective studies are certainly needed to better define the optimal threshold of scar burden above which CRT is unlikely to result in significant reverse remodeling.

Female sex was a strong and independent predictor of outcome in the total population and of the extent of reverse remodeling in the subgroup of patients with nonischemic cardiomyopathy. Epidemiological (24) and placebo-controlled clinical (25–27) trials have demonstrated that women with heart failure generally have a better survival than men, irrespective of the underlying etiology. However, to our knowledge, only 1 other observational registry has reported on sex-related differences in LV reverse remodeling after CRT (28). The exact mechanism by which female patients with nonischemic cardiomyopathy experience a better response is yet unclear and deserves further investigation.

Finally, in patients with QRS duration <140 ms before CRT not only did less reverse remodeling develop, but they also experienced a worsened outcome. Although several reports emphasized the limitations of QRS duration alone as a surrogate for electromechanical dyssynchrony and predictor of CRT response, some studies suggest that QRS width is a more robust predictor with increasing QRS duration (5,8).

Our data as well as data from the RethinQ trial, which failed to demonstrate improved response rates to CRT when adding echocardiographic measures of dyssynchrony (19,29) to a QRS duration <120 ms, suggest that QRS duration remains important and should not be marginalized as a implantation criterion.

Interestingly, although patients with a higher baseline LVESVi had a worse outcome, the baseline LVESVi itself was not an independent predictor of the overall course of LV remodeling. When we looked at late changes in the LVESVi (late is defined as >180 days) alone, we found a weak but significant trend in patients with a higher baseline LVESVi toward the development of late recurrent LV dilation. Other clinical variables, however, were not clearly associated with the course of remodeling >180 days after implantation. This again suggests that the early effect of CRT is important for the long-term outcome in CRT patients. After the first 6 months, changes become much less pronounced and do not seem to be strongly influenced by a pre-procedure variable.

Study limitations. A substantial proportion of patients who underwent CRT implantation at the Cleveland Clinic were not included in the analysis. The most common reason for exclusion was the lack of follow-up, which reflects the nature of the institution as a tertiary referral center. Although baseline characteristics and survival were fairly similar between the study population and the excluded patients, a selection bias cannot be excluded.

Although reverse remodeling with a nonischemic heart failure etiology was more pronounced in women, it was very similar in men and women with an ischemic etiology. However, the number of women with an ischemic etiology was small, and further studies are needed to clarify this issue.

The optimal break point was selected from among 4 alternatives using the optimal minimal likelihood ratio, although this selection method does not ensure that the selected point was significantly different from other possible break points.

Finally, this was a retrospective observational study, implying that treatment changes during follow-up may have influenced outcomes. However, to include these effects in the statistical model would have made the analysis even more complicated. In addition, we believe that the observational nature of the study makes the results more representative of real-world clinical practice.

Conclusions

Follow-up and monitoring of LV volume changes in patients undergoing CRT provides incremental evidence of an unfavorable course of LV remodeling in patients destined for potentially adverse outcomes. Factors associated with less reverse remodeling include ischemic etiology, male sex, and QRS duration <140 ms before implantation. In the majority of patients, a break point is observed at 6 months of CRT, after which favorable remodeling becomes much less pronounced.

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Key Words: cardiac resynchronization therapy ■ heart failure ■ remodeling.

APPENDIX

For statistical methods, please see the online version of this article.