Impact of Mitral Regurgitation on Reverse Remodeling and Outcome in Patients Undergoing Cardiac Resynchronization Therapy

Verhaert et al: Mitral regurgitation and CRT

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Abstract

**Background**—MR is associated with reduced survival in patients with chronic heart failure, but may be improved with CRT. We sought to evaluate the relationship between serial measurements of functional mitral regurgitation (MR) and reverse remodeling and outcomes in patients undergoing cardiac resynchronization therapy (CRT).

**Methods and Results**—266 consecutive patients undergoing 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. Temporal changes in MR severity and left ventricular end systolic volume index (LVESVi) were evaluated by linear mixed model analysis. CRT led to immediate sustained decrease in MR (p <0.0001) with no significant subsequent change. The amount of MR decrease correlated with a greater decrease in LVESVi late (p = <0.0001), but not early (p = 0.14) after CRT start. Patients with severe MR pre CRT experienced larger LVESVi decrease (p=0.005). Whereas baseline MR severity was not associated with adverse events (p=0.13), larger MR decrease (p = 0.001) and smaller residual MR after the initial 6 months of CRT (p = 0.03) were predictive of better outcome in a multivariable model.

**Conclusions**—Early reversal of functional MR was associated with reverse cardiac remodeling and improved outcomes. Patients with moderately severe to severe MR prior to CRT experienced relatively more reverse remodeling than patients with lesser degrees of MR.

**Key Words:** cardiac resynchronization therapy, mitral regurgitation, heart failure, remodeling
Functional mitral regurgitation (MR) is widely accepted as a strong predictor of outcome in patients with systolic heart failure.\textsuperscript{1-4} The presence of MR in chronic left ventricular (LV) dysfunction reflects an imbalance between closing forces acting on the mitral leaflets and tethering forces related to papillary muscle displacement.\textsuperscript{6-8} Previous studies have shown that cardiac resynchronization therapy (CRT) may improve the degree of MR, both immediately (by resynchronization of the papillary muscles and by causing an acute increase in LV closing force) as well as in the longer term as a consequence of reverse remodeling (resulting in a reduction of mitral valve tethering forces).\textsuperscript{9-13}

Patients with significant MR and advanced LV dysfunction, especially those with wide QRS morphology, pose a particularly difficult management dilemma as the benefits of surgical repair for correction of the MR in this population have been equivocal.\textsuperscript{14} With the advent of CRT and its anticipated benefits on functional MR via correction of the underlying ventricular dyssynchrony it would seem appropriate that CRT should be considered first line therapy, with surgical repair reserved for those not responding to CRT.

We therefore sought to examine the importance of both pre-existing MR as well as early and late changes in MR severity on long-term reverse remodeling with CRT, and hypothesized that significant reductions in mitral regurgitation leading to reverse remodeling can be detected early after CRT implantation, thereby providing guidance for further management.
Methods

The study protocol was approved by the Cleveland Clinic Institutional Review Board.

Study population and study design

We assessed patients that underwent first CRT device implantation at the Cleveland Clinic between January 2003 and June 2006, and who had a minimal echocardiographic follow-up of 90 days. Patients with a major event during these first 3 months (early death or urgent transplantation) were excluded. 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. As our goal was to assess functional MR (i.e. regurgitation occurring as a consequence of LV systolic dysfunction despite a structurally normal mitral valve) we excluded from the original population the patients with significant organic (structural) mitral valve disease, or history of mitral valve repair or replacement.

Demographic and clinical data were extracted from medical records. The etiology of heart failure was considered ischemic on the basis of a documented clinical history of prior myocardial infarction (with ECG evidence of infarct location) or a history of prior revascularization. The events were ascertained using the Social Security Death Index and reviewing patients’ electronic case records.

Echocardiographic analysis

All echocardiographic studies were digitally stored and measured off-line using Prosolv Cardiovascular software (Fuji Inc., Jp). “Early post-CRT studies” were defined as studies performed within the first 6 days after CRT implantation with the date of implantation being
time 0. Conventional 2- and 4 chamber images were used to calculate left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV) and ejection fraction (LVEF) using Simpson’s biplane method. All volumes were indexed according to body surface area. Left atrial size was assessed by left atrial area. The severity of MR was quantitated by vena contracta (VC), i.e. width of the neck or narrowest portion of the regurgitant jet.

Additionally, we calculated of the ratio of the jet area to the left atrial area, and the effective regurgitant orifice area (ERO). For VC and ERO measurements, if two jets were present, the dominant was taken as representative. Each of these three quantitative measurements was then transformed into semi-quantitative, five-point grading scale (0 to 4) using following cutoff values: 0, <10%, 10-20%, 20-45%, >45% for jet area/LA area; 0, <3 mm, 3-5 mm, 5-7 mm, >7 mm for VC; and 0, <0.15 cm², 0.15-0.29 cm², 0.30-0.40 cm², > 0.40 cm² for ERO. The value of three individual grades were then combined into a single MR grade (by calculating their median, determined using MS Excel software, Microsoft Corp. Wa), which was then used in survival analysis.

To assess inter- and intra-observer variability of vena contract measurements, we analyzed twelve studies obtained in six patients, with each patient contributing two studies, one of them being pre CRT. From each study we selected the representative multiple-beat clip showing vena contracta. Studies were measured by two independent observers and by a single observer after a time interval of one month. For each study, maximum vena contracta was measured in mid systole in two consecutive beats during separate sessions for each of the two beats. To assess the observer variability while including the impact of beat to beat variability, we calculated the absolute difference in VC measurement obtained during first of the two consecutive beats by first observer, with VC measurement obtained during second beat by a second observer. Analogous
process was used for intraobserver variability. To assess the observer variability after excluding impact of beat to beat variability, we calculated the absolute difference in VC measurement obtained during measurement of the first beat by two observers. Analogous process was used for intraobserver variability. Finally, to assess the inter-and intra-observer variability in the assessment of change in mitral regurgitation severity, we first calculated the difference in VC, measured during a first beat of the clip, between two studies obtained in a single patient. Inter- and intraobserver variabilities were calculated as described above.

**Statistical Analysis**

Data are presented as means ± SD, unless otherwise noted.

To assess the evolution of MR severity (assessed by VC) and LV end-systolic volume index (LVESVi) during CRT, we applied a Linear Mixed Effects model with unstructured covariance for random effects using SPSS (SPSS Inc. Chicago, IL). In a first step we assessed the impact of CRT on MR. Previous studies have shown that CRT leads to both immediate and late decrease of MR. To model the effects of CRT, we used a piecewise linear regression for both fixed and random effects. We tested the models with the breakpoint set up at the 3rd, 90th, 180th, and 360th day of CRT.

In a second step, we assessed the timed-dependent correlation between changes in MR and the amount of reverse remodeling during CRT. For this purpose, we used again Linear Mixed Effects model approach to correlate VC change from baseline with percent LVESVi change from baseline, with the time covariate set to zero if the data were assessed during first 7 days, and to one if otherwise.

In a third step we assessed if pre-CRT MR severity affects LV remodelling and left atrial remodelling during CRT. LV ESVi and left atrial area were used as markers of LV and left atrial...
remodelling, respectively. According pre-CRT MR, patients were divided into group with severe MR (MR grade >2) and group with no more than moderate MR (MR grade ≤2). We again used piecewise linear regression with the breakpoint set up at the 90th, 180th, and 360th day of CRT.23 15 For all linear mixed effects, Akaike information criterion was used to compare incremental value of models. Wald statistics was used to test for the difference in slopes of piecewise regression.23

Additional data are provided in Supplemental Material. To assess the prognostic value of baseline MR severity and MR severity during follow-up, we compared survival curves constructed by Kaplan Meier by log-rank statistics, with end point being a composite of death from any cause (determined by the Social Security Death Index), heart transplantation, or left ventricular assist device (LVAD) implantation. We also performed a stepwise Cox proportional hazards regression with the combined end-point of all-cause death, heart transplant or LV assist device implantation. Variables entered as potential predictors included, age, gender, NYHA class, QRS duration, heart failure etiology, lead position, MR severity and baseline LVESVi. In all analyses a p value of <0.05 was taken to represent significance.

Results

Patients

We identified 1067 patients with first CRT device implanted at Cleveland Clinic between January 2003 to June 2006. Out of these patients, 754 were excluded due to no echocardiogram available after >90 days of CRT (n = 721) or clinical event within first 90 days (33 patients). Out of remaining 313 patients, 44 patients had prior mitral valve surgery, two did not have adequate
echocardiograms for mitral regurgitation assessment, and one had mitral valve repair after the start of resynchronization therapy (Supplemental Figure 1), leaving 266 patients to be analyzed. None of these patients had structural mitral valve disease. In 155 (58%) subjects echocardiography within the first 6 days (mean 2.2 ± 3.3 days) after CRT implant was performed. One hundred thirteen patients experienced >15% reduction in LVESVi 82 patients had 0-15 % reduction in LVESVi and 71 patients had an increase in LVESVi in spite of CRT. The baseline characteristics of our study population are described in the Table. The majority of our patients had trivial or mild MR, with most jets being central. As it is often impossible to assess ERO in the setting of low MR grade, and because of known sensitivity of jet area/LA area to technical issues such as gain settings and jet direction, we used VC as a quantitative marker of MR severity, with ERO and jet area/LA area used only for determining MR grade.

Changes in MR severity during CRT

MR severity assessed by VC promptly decreased with CRT. The best model for describing temporal change of MR severity during CRT was a piecewise regression with a breakpoint at day 3 (Figure 1) with a significant early decrease in MR (VC decrease of 0.8 mm, p =<0.0001), and no significant change during follow-up.

Figure 2 shows the relationship between VC change and percent LVESVi change early (during first 7 days; Panel A) and late (after > 7 days; panel B) after the start of CRT. Early after CRT start there was no correlation between VC change and percent ESVi change (p = 0.14), with most large proportion of patients experiencing VC decrease without significant LVESVi change. In contrast, during late follow up there was a significant correlation between these two parameters.
(p<0.0001), with significant decrease in both percent LVESVi and VC. In summary, early MR improvement was followed by LV reverse remodelling.

**Impact of pre-CRT MR on left ventricular and left atrial remodelling**

Figure 3 shows the impact of baseline (pre-CRT) MR severity on LV remodelling. As previously shown, the best model for describing temporal change of LV ESVi during CRT was a piecewise regression with a breakpoint at 3 months. While LV ESVi decreased in both groups (p <0.0001), reverse remodeling during initial 3 months was more pronounced in patients with more severe baseline MR (p=0.005). Interestingly, while there was a trend towards higher left atrial areas in patients with more severe baseline MR (28.5±5.9 vs 26.7±6.7 cm², p = 0.09), no changes within- or between-groups were observed during follow up.

**Impact of MR severity on outcome in patients undergoing CRT**

During the average clinical follow-up of 3.6 ± 1.6 years (range 111 – 2,192 days), 95 patients reached the combined endpoint (including 78 deaths, 14 heart transplantation, and 3 LVAD implantations). In our study cohort, baseline MR severity (dichotomized by the presence or absence of more than 2+ MR) was not predictive of outcome by univariable Cox proportional hazards analysis (HR 0.59; 95% CI 0.30-1.18, p =0.13) (Figure 4).

In the next step we analyzed if survival is related to either decrease in MR grade or MR grade during CRT. For this purpose we determined the minimal MR grade observed at any time during first 6 months of treatment. As in this period five patients died, while 37 patients did not have adequate echocardiogram performed during first six months they were excluded from the analysis, leaving the final group of 224 patients. Both the decrease in MR grade (p =0.001; HR 0.64, 95%CI 0.50-0.83) and MR grade during CRT (p = 0.03, HR 1.27, 95%CI 1.02-1.58) were
independent predictors in a multivariable stepwise Cox model that included relevant clinical variables. Figure 5 shows that patients with MR grade 2+ or less during first six months CRT had significantly better survival.

**Intra- and interobserver variability**

Intra- and interobserver variability for the measurement of VC, while including the impact of beat to beat variability, was 1.6±1.3 mm and 1.7±1.2 mm, respectively. Intra- and interobserver variability for the measurement of VC, while excluding the impact of beat to beat variability, was 1.0 ±0.8 mm and 1.1±1.0 mm, respectively. Intra- and interobserver variability for the measurement of change in VC was 2.0±1.4 mm and 2.1±1.7 mm, respectively.

**Discussion**

The novel findings of our study are that most of the decrease in MR during CRT occurs within days of initiation of biventricular pacing. In fact, we have not shown any further significant MR decrease during follow up. Furthermore, we have shown that while early after beginning of CRT there is no correlation between MR decrease and LVESVi decrease, this correlation becomes apparent at later follow up, implying the role of early VC in reverse LV remodelling. Finally, patients with significant (>2+) MR pre-CRT experienced more reverse remodelling, indicating that severe functional MR does not interfere with the effects of CRT.

As early MR decrease precedes subsequent LV remodelling (Figures 1 to 3), it appears that there is a both a statistical and biological interaction between amount of LV remodelling and MR during CRT, where immediate MR decrease heralds subsequent reverse remodelling. Of note, an
average decrease of close to 2 mm in VC, that was observed in patients with most remodelling, is both clinically relevant and can be detected in individual patients.

Immediate versus late effects of CRT on MR severity

While CRT decreases both MR and LV volumes, it has been shown that an immediate decrease of MR occurs before any significant LV remodelling. Possible mechanisms include an increase in the rate of LV pressure rise which counteracts tethering forces and leads to more effective mitral valve closure and improved papillary muscle dyssynchrony. This immediate change in MR could be expected to have some prognostic significance. Surprisingly, the analysis of REVERSE data did not show correlation between immediate MR decrease and subsequent LV remodelling. Possible reasons are inclusion of patients with no or mild symptoms, MR presence in minority of patients, and method used for MR quantitation. In contrast, our findings show the link between MR decrease and LV remodelling. While MR decrease preceded LV remodelling, there was a clear correlation between late changes in MR and LVESVi, with larger MR decrease leading to larger LVESVi decrease. Assuming that early MR decrease is stable during late follow-up, which is supported by our data, this temporal sequence suggests that early MR decrease may play a role in reverse remodelling of the left ventricle.

Reverse LV remodelling, survival and the impact of mitral regurgitation before and immediately after the start of CRT. While functional MR in patients with heart failure conveys an adverse prognosis, our study implies that severe pre-implant MR may not necessarily predict worse outcome in patients with heart failure undergoing CRT. Indeed, patients with pronounced baseline MR in our series experienced more reverse remodelling. Of note, our
analysis did not take into account other factors that may influence remodelling, and analysis of echocardiography data from CARE-HF trial showed that baseline MR is not a predictor of remodelling in a multivariate analysis.\textsuperscript{26} However, these findings, in addition to our findings of the absence of the impact of baseline MR on survival, indicate that CRT can be safely implemented even in the setting of severe functional MR.

In contrast, presence of >2+ MR after initial 6 months of CRT was found to be predictive of adverse events, which is consistent with a CARE–HF data.\textsuperscript{22} The decrease of MR during CRT can be interpreted as a surrogate index of both LV remodeling and resynchronization.

Interestingly, the relative contribution of LV reverse remodelling and resynchronization to survival benefit brought by CRT is controversial. For example Ypenburg et al. showed that prognosis after CRT is related to the extent of LV reverse remodeling,\textsuperscript{27} while CARE-HF substudy showed that survival benefit from CRT was not significantly different between nonischemic (hazard ratio 0.46) and ischemic (hazard ratio 0.71) patients (p = 0.06) despite nonischemic patients having much more reverse remodelling.\textsuperscript{28} On the other hand, one can argue that the study was underpowered, as difference in hazard ratios of 0.25 is not clinically irrelevant; further studies will be necessary to answer this question.

**Strengths and Limitations**

Major strengths of this study are a large sample size, digital data analysis, MR quantitation by VC, and longitudinal approach to data evaluation that enabled us to construct the shape of the average trajectory of the change in LV ESVi and MR severity during CRT. While several prospective randomized CRT trials that serially assessed MR are superior to our study by the number of patients and the prospective nature of the design, they invariably used ratio between
regurgitant jet and left atrial area as a marker of MR severity which is known to be affected by multiple technical issues, and were often performed off of videotapes which have more than two times lower linear resolution than digital data.\textsuperscript{25-26, 29}

Our major limitations are that our study was retrospective and observational with population comprised of patients with clinical and echocardiographic follow-up in a tertiary care center, and a selection bias cannot be excluded. Patients with a major adverse event within the first 90 days of implantation were not included in this study, as we were particularly interested in the effects of mitral regurgitation on long-term reverse remodeling. One could argue that these patients are early non-responders and the role of MR in the lack of response to CRT in this group remains speculative. Only a proportion of patients underwent echocardiography in the first few days after implantation, which may have influenced our observation on the early effect of CRT on MR. Information on the development of atrial fibrillation and the proportion of effective biventricular pacing in our study population was not available, although this may have represented another potentially important mediator of response and outcome. We used left atrial area to as a measure of its size instead of indexed left atrial volumes, which is a less precise method. We have not quantitated the number of mitral regurgitation jets, or whether the presence of multiple jets is a predictor of the outcome of CRT. However, all of our patients had functional MR, which should decrease variability of MR characteristics.

Finally, this was an observational study implying that changes in pharmacologic or non-pharmacologic therapies during follow-up may have influenced MR severity, outcome and remodeling. However, to include these effects in the statistical model would have made the analysis more complex. In addition, we believe that the observational nature of the study makes the results representative of real-world clinical practice.
Clinical implications

MR is widely prevalent among patients with dilated ischemic or non-ischemic cardiomyopathy, and is generally associated with poor outcome. As long-term survival in this population does not appear to be improved by mitral valve annuloplasty 14 alone, CRT may offer a valid alternative in the absence of organic mitral valve lesions. The ability to detect reductions in MR severity within the first week of CRT implantation provides an early insight into the potential clinical response to CRT. Furthermore it provides another functional parameter to target for optimization of pacing intervals and configurations.

Conclusions

Early reduction of MR appears to be associated with a greater potential decrease in LVESVI. Furthermore, the presence of significant MR in patients who are otherwise candidates does not preclude CRT response. Finally, the presence of greater than moderate MR after the 6 month mark portends adverse long-term outcome.
Sources of Funding

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Disclosures

Dr Richard A. Grimm is consultant for Medtronic, St. Jude Medical and GE Healthcare. Dr. Bruce L.Wilkoff is consultant for Medtronic, St. Jude Medical and Boston Scientific. Dr. W.H. Wilson Tang is a consultant for Medtronic.
References


Table. Baseline characteristics of the study cohort (n = 266)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender (%)</td>
<td>69</td>
</tr>
<tr>
<td>Ischemic etiology (%)</td>
<td>51</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.2±11.8</td>
</tr>
<tr>
<td>NYHA class II/III/IV (%)</td>
<td>10/81/9</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>25±9</td>
</tr>
<tr>
<td>LVESVi (mL/m²)</td>
<td>94±40</td>
</tr>
<tr>
<td>Left atrial area (cm²)</td>
<td>27±7</td>
</tr>
<tr>
<td>VC (mm)</td>
<td>3.5±2.4</td>
</tr>
<tr>
<td>MR severity (0/1+/2+/3+/4+)</td>
<td>76/84/66/27/13</td>
</tr>
<tr>
<td>Sinus Rhythm (%)</td>
<td>81</td>
</tr>
<tr>
<td>QRS width (ms)</td>
<td>162±28</td>
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<tr>
<td>LBBB or continuous RV pacing (%)</td>
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<td>ICD (%)</td>
<td>93</td>
</tr>
<tr>
<td>ACE/ARB</td>
<td>(86%)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>(85%)</td>
</tr>
<tr>
<td>Posterior/Lateral/Anterior lead position (%)</td>
<td>68/28/4</td>
</tr>
</tbody>
</table>

Continuous variables are represented as mean ± SD, categorical variables as %.

**Abbreviations**: ARB: angiotensin receptor blockers; ACE: angiotensin converting enzyme inhibitors; ICD: intracardiac defibrillator; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction, LVESVi: left ventricular end-systolic volume index at baseline, NYHA: New York Heart Association functional class, RV: right ventricle; VC: width of the mitral valve regurgitant jet at the vena contracta
Figure Legends

Figure 1. Estimated course of MR severity (measured as vena contracta width, VC) for the entire study cohort. Markers represent the average of the observed data obtained at pre-implant (time zero), and during follow-up. Error bars represent 95% confidence intervals. The piecewise regression line is obtained by mixed model approach (see Statistical Methods for details).

Figure 2. Relationship between change in MR severity (measured as vena contracta width, VC) and percent change in left ventricular end-systolic volume index (LVESVi) early during first 7 days (Panel A), and late (Panel B) after the start of cardiac resynchronization therapy. Early after the start of therapy only vena contracta decrease is seen with no correlation between vena contracta change and end-systolic volume change. In contrast, late after the start of treatment there is a decrease in end-systolic volume index that correlates with vena contracta decrease (p < 0.0001).

Figure 3. Estimated course of left ventricular end-systolic volume index change (LVESVi) for patients with >2+ MR (n=40) versus patients with ≤2+ MR (n=226) prior to CRT. The piecewise regression line is again obtained by mixed model analysis. Error bars represent 95% confidence intervals. Patients with >2+MR prior to CRT show a larger initial LVESVi decrease (p=0.005).
Figure 4. Kaplan-Meier survival curves for patients with > 2+ MR (n=40) versus patients with ≤ 2+ MR (n=226) prior to CRT. Event-free survival was defined as freedom from death, HRT or need for LVAD.

Figure 5. Kaplan-Meier survival curves for patients with > 2+ MR (n=30) versus patients with ≤ 2+ MR (n=194) after 6 months of CRT. Event-free survival was defined as freedom from death, HRT or need for LVAD.
Figure 1

Follow-up (Days)

VC (mm)

p = 0.0001

n = 266 168 107 154 199 170
Figure 2

A

Early VC change (mm)

Early LVESVi change (%)

p = 0.14

B

Late VC change (mm)

Late LVESVi change (%)

p < 0.0001
Figure 3

- Baseline MR >2
- Baseline MR ≤2

p <0.0001 for ESVI decrease
p = 0.005 for interaction

Baseline MR >2: 40 24 16 25 35 29
Baseline MR ≤2: 226 144 91 129 164 141
Figure 4

Event-Free Survival

Time (Days)

Baseline MR>2

Baseline MR≤2

No at risk:

Baseline MR>2  40  35  32  15  8
Baseline MR≤2  226  202  171  78  32

p = 0.13
Figure 5

Event-Free Survival

MR 6 Months post CRT ≤2

MR 6 Months post CRT >2

p < 0.0001

No at risk:
Post CRT MR>2 30 22 13 7 3
Post CRT MR≤2 194 182 160 65 27
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Supplemental Material

Statistical Methods:

To assess the evolution of vena contracta (VC) and LV end-systolic volume index (LVESVi) during cardiac resynchronization therapy (CRT), we applied Linear Mixed Effects model with unstructured covariance for random effects, and with time as a covariate, using SPSS (SPSS Inc. Chicago, IL). This approach allows for longitudinal assessment of data that are repeatedly measured in the same individuals. This method, in contrast to repeated measures analysis of variance, is less sensitive to missing data, can accommodate an uneven number of data points, and is not bound by a specific structure of variance/covariance matrix. In this way, a truly longitudinal approach of changes in cardiac function and structure during CRT treatment can be applied that is robust in the setting of a natural patient loss due to a disease.

We firstly assessed the global impact of CRT on VC. We assumed that CRT leads to prompt early decrease of VC, with much less pronounced changes during late follow up. However, the exact breakpoint between these two parts of the curve was unknown, and it was uncertain whether the late slope of this relationship is different from zero. Therefore, piecewise linear regression was used to model the effect of time for both fixed and random effects: using the equation:

\[
E(Y_{ij} \mid b_i) = B_1 + B_2t_{ij} + B_3(t_{ij} - n)_+ + b_1 + b_2t_{ij} + b_3(t_{ij} - n)_+ 
\]

where \(B_1...n\) denotes fixed effects, \(b_1...n\) denotes random effects, \(t_{ij}\) denotes time in days, \(n\) denotes days that were tested as potential breakpoints in the piecewise linear regression
the values tested being 90, 180, 360 and 720 days) and \((t_{ij} - n)_+\) equals \(t_{ij} - n\) if \((t_{ij} - n) > 0\) or 0 otherwise. An optimal breakpoint was selected as the one that resulted in a minimal likelihood ratio of the model. The difference between \(B_2\) and \(B_3\) (i.e. whether late slope was horizontal, upward or downward) was tested by Wald statistics. If there was no difference, the equation was simplified by replacing \(B_2t_{ij} + B_3(t_{ij} - n)_+\) with \(B_4(t_{ij} + (t_{ij} - n)_+)\).

Additionally, we assessed whether the group of patients with initially severe mitral regurgitation differ from group with mild to moderate mitral regurgitation in the amount of LV remodelling (change in LVESVi) during CRT. For this purpose, we changed the initial equation to encompass the effect of two groups:

\[
E(Y_{ij} \mid b_i) = B_1 + B_2t_{ij} + B_3(t_{ij} - n)_+ + B_4 \times \text{Group} + B_5 \text{Group} \times t_{ij} + B_6 \text{Group} \times (t_{ij} - n)_+ + b_1 + b_2t_{ij} + b_3(t_{ij} - n)_+ \]

Again, the difference between \(B_2\) and \(B_3\) and between \(B_5\) and \(B_6\) (i.e. whether the late slope was horizontal, upward or downward sloping) was tested by Wald statistics. If slopes were horizontal, they were replaced in a manner analogous to above.

Finally, we assessed the relationship between VC change from baseline with percent LVESVi:

\[
E(Y_{ij} \mid b_i) = B_1 + B_2 \times \text{VC} + B_3t_{ij} + + B_4 \times \text{VC} \times t_{ij} \]

Where \(t_{ij} = 0\) for the first 7 days, and 1 otherwise.

In all analyses a p value of <0.05 was taken to represent significance.
References


**Legend for Supplemental Figure 1.** Patient enrollment along with reasons for exclusion from the final group. CRT: cardiac resynchronization therapy. LVAD: left ventricular assist device
1067 CRT patients from 1/2003 to 6/2006

754 excluded:
- 33 transplant, LVAD or death within 90 days
- 721 no echo after 90 days

313 with echo ≥90 days

47 excluded:
- 37 prior mitral valve repair
- 7 prior mitral valve replacement
- 2 inadequate echo
- 1 mitral valve repair post CRT

266 patients studied

Supplemental Figure 1.