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

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

Methods and Results—A total of 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 (LV) assist device. Temporal changes in MR severity and LV end-systolic volume index (LVESVi) were evaluated by linear mixed-model analysis. CRT led to an 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 began. Patients with severe MR before CRT experienced a larger LVESVi decrease (p=0.005). Although baseline MR severity was not associated with adverse events (p=0.13), a larger MR decrease (p=0.001) and a 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 before CRT experienced relatively more reverse remodeling than patients with lesser degrees of MR. (Circ Cardiovasc Imaging. 2012;5:21-26.)

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.1–5 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.6–9 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 a short-term increase in LV closing force) and in the longer-term as a consequence of reverse remodeling (resulting in a reduction of mitral valve tethering forces).9–13

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Patients with significant MR and advanced LV dysfunction, especially those with wide QRS morphological features, pose a particularly difficult management dilemma because the benefits of surgical repair for correction of the MR in this population have been equivocal.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 as first-line therapy, with surgical repair reserved for those not responding to CRT.

We, therefore, sought to examine the importance of both preexisting MR and early and late changes in MR severity on long-term reverse remodeling with CRT and hypothesized that significant reductions in MR, 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 who 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.15 Patients with a major event during these first 3 months (early death or urgent trans-
plantation) 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 (D.V. and Z.B.P.). Because our goal was to assess functional MR (ie, 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 cause of heart failure was considered ischemic on the basis of a documented clinical history of myocardial infarction (with ECG evidence of infarct location) or a history of 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; Tokyo, Japan). 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 LV end-diastolic volume, LV end-systolic volume (LVESVi), and LV ejection fraction using the Simpson biplane method.16 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; ie, width of the neck or narrowest portion of the regurgitant jet).17–19 In addition, we calculated the ratio of the jet area/left atrial area and the effective regurgitant orifice area (ERO).7,22 For VC and ERO measurements, if 2 jets were present, the dominant was that of the neck or narrowest portion of the regurgitant jet.17–19

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Additional data are provided in the Online Only Data Supplement. 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 the end point being a composite of death from any cause (determined by the Social Security Death Index), heart transplantation, or LV assist device implantation. We also performed a stepwise Cox proportional hazards regression with the combined end point of all-cause death, heart transplantation, or LV assist device implantation. Variables entered as potential predictors included age, sex, New York Heart Association class, QRS duration, heart failure cause, lead position, MR severity, and baseline LVESVi.

In all analyses, P<0.05 was significant.

**Results**

**Patients**

We identified 1067 patients with a first CRT device implanted at the Cleveland Clinic between January 2003 and June 2006. Of these patients, 754 were excluded because no echocardiogram was available after >90 days of CRT (n=721) or a clinical event occurred within the first 90 days (n=33). Of the remaining 313 patients, 44 had prior mitral valve surgery, 2 did not have adequate echocardiograms for MR assessment, and 1 had mitral valve repair after the start of resynchronization therapy (Online Only Data Supplement Figure 1), leaving 266 patients to be analyzed. None of these patients had structural mitral valve disease. In 155 (58%) of the subjects, echocardiography within the first 6 days (2.2±3.3 days) after CRT implantation was performed. A total of 113 patients experienced >15% reduction in LVESVi (82 had a 0%–15% reduction in LVESVi); 71 patients had an increase in LVESVi, despite CRT. The baseline characteristics of our study population are described in the Table. Most of our patients had trivial or mild MR, with most jets being central. Because 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 break point at day 3 (Figure 1), with a significant early decrease in MR (VC decrease, 0.8 mm; P=0.0001), and no significant change during follow-up.

Figure 2 shows the relationship between VC change and percentage LVESVi change early (during the first 7 days, Figure 2A) and late (after >7 days, Figure 2B) after the start of CRT. Early after the start of CRT, there was no correlation between changes in MR and the amount of reverse remodeling during CRT. For this purpose, we again used a linear mixed-effects model approach to correlate VC change from baseline with percentage LVESVi change from baseline, with the time covariate set to 0 if the data were assessed during the first 7 days and to 1 if otherwise.

In a third step, we assessed if pre-CRT MR severity affects LV remodeling and left atrial remodeling during CRT. LVESVi and left atrial area were used as markers of LV and left atrial remodeling, respectively. According to pre-CRT MR, patients were divided into a group with severe MR (MR grade >2) and a group with no more than moderate MR (MR grade ≤2). We again used piecewise linear regression with the break point set up at the 90th, 180th, and 360th day of CRT.18–21 For all linear mixed effects, the Akaike information criterion was used to compare the incremental value of models. Wald statistics was used to test for the difference in slopes of piecewise regression.23

Additional information is provided in the Online Only Data Supplement.
between VC change and percentage ESVi change ($P=0.14$), with most patients experiencing a VC decrease without a significant LVESVi change. In contrast, during late follow-up, there was a significant correlation between these 2 parameters ($P<0.0001$), with a significant decrease in both percentage LVESVi and VC. In summary, early MR improvement was followed by LV reverse remodeling.

### Impact of Pre-CRT MR on LV and Left Atrial Remodeling

Figure 3 shows the impact of baseline (pre-CRT) MR severity on LV remodeling. As previously shown, the best model for describing temporal change of LVESVi during CRT was a piecewise regression with a break point at 3 months. Although LVESVi decreased in both groups ($P<0.0001$), reverse remodeling during the initial 3 months was more pronounced in patients with more severe baseline MR ($P=0.005$). Interestingly, although there was a trend toward higher left atrial areas in patients with more severe baseline MR ($28.5 \pm 5.9$ versus $26.7 \pm 6.7 \text{ cm}^2; P=0.09$), no changes within or between groups were observed during follow-up.

### Impact of MR Severity on Outcome in Patients Undergoing CRT

During the clinical follow-up of $3.6 \pm 1.6$ years (range, 111–2192 days), 95 patients reached the combined end point (including 78 deaths, 14 heart transplantations, and 3 LV assist device implantations). In our study cohort, baseline MR severity (dichotomized by the presence or absence of $\geq 2+$ MR) was not predictive of outcome by univariable Cox proportional hazards analysis (hazard ratio [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

### Table. Baseline Characteristics of the Study Cohort ($N=266$)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, %</td>
<td>69</td>
</tr>
<tr>
<td>Ischemic cause, %</td>
<td>51</td>
</tr>
<tr>
<td>Age, y</td>
<td>$64.2 \pm 11.8$</td>
</tr>
<tr>
<td>NYHA functional class II/III/IV, %</td>
<td>$10/81/9$</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>$25 \pm 9$</td>
</tr>
<tr>
<td>LVESVi, mL/m$^2$</td>
<td>$94 \pm 40$</td>
</tr>
<tr>
<td>Left atrial area, cm$^2$</td>
<td>$27 \pm 7$</td>
</tr>
<tr>
<td>VC, mm</td>
<td>$3.5 \pm 2.4$</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>$162 \pm 28$</td>
</tr>
<tr>
<td>LBBB or continuous RV pacing, %</td>
<td>71</td>
</tr>
<tr>
<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, and categorical variables are represented as percentages.

ACE indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICD, intracardiac defibrillator; LBBB, left bundle branch block; LVEF, LV ejection fraction; NYHA, New York Heart Association; RV, right ventricle.
any time during the first 6 months of treatment. During this period, 5 patients died, whereas 37 patients did not have an adequate echocardiogram performed during the first 6 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 an MR grade of $\geq 2$ during the first 6 months of CRT had significantly better survival.

Intraobserver and Interobserver Variability

Intraobserver and interobserver variabilities for the measurement of VC, while including the impact of beat-to-beat variability, were $1.6_{0.1.3}$ and $1.7_{0.1.2}$ mm, respectively. Intraobserver and interobserver variabilities for the measurement of VC, while excluding the impact of beat-to-beat variability, were $1.0_{0.8}$ and $1.1_{0.1.0}$ mm, respectively. Intraobserver and interobserver variabilities for the measurement of change in VC were $2.0_{1.4}$ 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, although early after starting CRT, there is no correlation between MR decrease and LVESVi decrease, this correlation becomes apparent at later follow-up, implying the role of early MR in reverse LV remodeling. Finally, patients with significant ($\geq 2$) MR pre-CRT experienced more reverse remodeling, indicating that severe functional MR does not interfere with the effects of CRT.

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

Immediate Versus Late Effects of CRT on MR Severity

Although CRT decreases both MR and LV volumes, an immediate decrease of MR occurs before any significant LV remodeling. Possible mechanisms include an increase in the rate of LV pressure increase, 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 Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study data did not show a correlation between immediate MR decrease and subsequent LV remodeling. Possible reasons are inclusion of patients with no or mild symptoms, MR presence in
a few patients, and method used for MR quantitation. In contrast, our findings show the link between MR decrease and LV remodeling. Although an MR decrease preceded LV remodeling, there was a clear correlation between late changes in MR and LVEFVi, with a larger MR decrease leading to a larger LVEFVi decrease. Assuming that an early MR decrease is stable during late follow-up, which is supported by our data, this temporal sequence suggests that an early MR decrease may play a role in reverse remodeling of the left ventricle.

**Reverse LV Remodeling, Survival, and the Impact of MR Before and Immediately After the Start of CRT**

Although functional MR in patients with heart failure conveys an adverse prognosis, our study implies that severe preimplantation 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 remodeling. Our analysis did not account for other factors that may influence remodeling, and analysis of echocardiographic data from the Cardiac Resynchronization in Heart Failure trial showed that baseline MR is not a predictor of remodeling in a multivariate analysis. 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, the presence of >2+ MR after the initial 6 months of CRT was predictive of adverse events, which is consistent with Cardiac Resynchronization in Heart Failure data. 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 remodeling 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, whereas the Cardiac Resynchronization in Heart Failure substudy showed that survival benefit from CRT was not significantly different between nonischemic (HR, 0.46) and ischemic (HR, 0.71) patients ($P=0.06$), despite nonischemic patients having much more reverse remodeling. On the other hand, the study may have been underpowered, because a difference in HRs of 0.25 is not clinically irrelevant; further studies will be necessary to answer this question.

**Strengths and Limitations**

The major strengths of this study are a large sample size, digital data analysis, MR quantitation by VC, and a longitudinal approach to data evaluation that enabled us to construct the shape of the average trajectory of the change in LVEFVi and MR severity during CRT. Although 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 >2 times lower linear resolution than digital data.

Our major limitations are that our study was retrospective and observational, with a population composed 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, because we were particularly interested in the effects of MR on long-term reverse remodeling. These patients may be early nonresponders, 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 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 MR 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 the variability of MR characteristics.

Finally, this was an observational study implying that changes in pharmacological or nonpharmacological 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-life clinical practice.

**Clinical Implications**

MR is widely prevalent among patients with dilated ischemic or nonischemic cardiomyopathy and is generally associated with poor outcome. Because long-term survival in this population does not appear to be improved by mitral valve annuloplasty 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 LVEFVi. 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 an adverse long-term outcome.

**Sources of Funding**

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**Disclosures**

Dr Wilkoff is a consultant for Medtronic, St Jude Medical, and Boston Scientific; Dr Wilson Tang is a consultant for Medtronic; and Dr Grimm is a consultant for Medtronic, St Jude Medical, and GE Healthcare.

**References**


We assessed the interplay of mitral regurgitation (MR) and cardiac resynchronization therapy (CRT) in 266 consecutive patients by looking at temporal changes in MR severity and left ventricular end-systolic volume index (LVESVi) during a follow-up that extended over several years. CRT led to an immediate and sustained decrease in MR ($P<0.0001$), with no significant change during late follow-up, whereas LVESVi increased slowly over the first several months, to become stable during late follow-up. The amount of MR decrease correlated with a greater decrease in LVESVi late, but not early, after CRT. Patients with severe MR pre-CRT experienced a larger LVESVi decrease. Although baseline MR severity was not associated with adverse events (defined as all-cause mortality, heart transplantation, or implantation of an LV assist device), larger MR decreases and less residual MR after the initial 6 months of CRT were predictive of better outcome in a multivariable model. In summary, early reversal of functional MR was associated with reverse cardiac remodeling and improved outcomes. Patients with moderately severe to severe MR before CRT experienced relatively more reverse remodeling than patients with lesser degrees of MR. 

**CLINICAL PERSPECTIVE**

We assessed the interplay of mitral regurgitation (MR) and cardiac resynchronization therapy (CRT) in 266 consecutive patients by looking at temporal changes in MR severity and left ventricular end-systolic volume index (LVESVi) during a follow-up that extended over several years. CRT led to an immediate and sustained decrease in MR ($P<0.0001$), with no significant change during late follow-up, whereas LVESVi increased slowly over the first several months, to become stable during late follow-up. The amount of MR decrease correlated with a greater decrease in LVESVi late, but not early, after CRT. Patients with severe MR pre-CRT experienced a larger LVESVi decrease. Although baseline MR severity was not associated with adverse events (defined as all-cause mortality, heart transplantation, or implantation of an LV assist device), larger MR decreases and less residual MR after the initial 6 months of CRT were predictive of better outcome in a multivariable model. In summary, early reversal of functional MR was associated with reverse cardiac remodeling and improved outcomes. Patients with moderately severe to severe MR before CRT experienced relatively more reverse remodeling than patients with lesser degrees of MR.
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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:

\[ E(Y_{ij} \mid b_i) = B_1 + B_2 t_{ij} + B_3 (t_{ij} - n) + b_1 + b_2 t_{ij} + b_3 (t_{ij} - n) \]

where \( B_1 \ldots n \) denotes fixed effects, \( b_1 \ldots n \) 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:

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

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.