Mechanistic Features Associated With Improvement in Mitral Regurgitation After Cardiac Resynchronization Therapy and Their Relation to Long-Term Patient Outcome

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Background—Mechanisms of mitral regurgitation (MR) reduction with cardiac resynchronization therapy (CRT) are complex, and their association with long-term outcome is unclear. We sought to elucidate mechanistic features of reduction in MR with CRT, which impact long-term patient survival.

Methods and Results—A prospective longitudinal study of 277 patients with heart failure with QRS width ≥120 ms and ejection fraction ≤35% for CRT was performed. Quantitative echocardiography, including dyssynchrony analysis, was performed at baseline. MR was quantified by color Doppler before and 6 months after CRT. Predefined end points of death, transplant, or left ventricular assist device were tracked during 4 years. There were 114 (48%) patients with CRT with significant MR (≥moderate) at baseline; of whom 48 (42%) patients had MR improvement, and 24 (19%) patients had MR worsening after CRT. The 66 events (47 deaths, 10 transplantations, and 9 left ventricular assist devices) were strongly associated with significant MR after CRT (hazard ratio, 3.58; 95% confidence interval, 2.18–5.87; P<0.0001). Three echocardiographic features were independently associated with amelioration of significant MR after CRT by multivariable analysis: anteroseptal to posterior wall radial strain dyssynchrony >200 ms, lack of severe left ventricular dilatation (end-systolic dimension index <29 mm/m²), and lack of echocardiographic scar at papillary muscle insertion sites (all P<0.05) and, when combined, were additively associated with long-term survival (P=0.0001).

Conclusions—Significant MR after CRT was strongly associated with less favorable long-term survival. Echocardiographic mechanistic features were identified that were associated with improvement in MR after CRT and favorable long-term survival. (Circ Heart Fail. 2013;6:685-693.)

Key Words: cardiac resynchronization therapy ■ echocardiography ■ mitral valve insufficiency

Mitral regurgitation (MR) in patients with heart failure (HF) is generally associated with a poor prognosis.

Cardiac resynchronization therapy (CRT) has been shown to reduce MR in patients with HF with widened QRS and systolic dysfunction, although results are variable. Despite significant clinical improvements from CRT, approximately one third of the patients do not seem to benefit from therapy. Several clinical variables, including lack of dyssynchrony, scar burden, and left ventricular (LV) lead position, have been associated with lack of CRT response. However, the impact of MR on clinical outcomes after CRT and factors associated with improvement in MR after CRT are not well understood. The objectives of this current study were to test the hypotheses that MR after CRT is associated with unfavorable clinical outcomes and that specific echocardiographic features may be identified before CRT that could be associated with improvements in MR and accordingly predictive of patient outcomes.

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Methods

We prospectively studied 302 consecutive patients referred for CRT with chronic severe HF despite optimal medical therapy (New York Heart Association class III or IV), LV ejection fraction (EF) ≤35%, and QRS duration >120 ms. The protocol was approved by the Institutional Review Board on Biomedical Research, and all patients gave informed consent consistent with this protocol. Patients with ≥50% stenosis of at least 1 major coronary artery and history of a documented myocardial infarction were considered as having ischemic disease. Exclusion criteria were a prosthetic mitral valve, mitral valve prolapse or flail segment, significant mitral stenosis, significant aortic stenosis, or regurgitation. All patients received a biventricular pacing defibrillator device for CRT with a right ventricular apical lead and LV pacing lead implanted through the coronary sinus in an epicardial vein, targeting the posterior or lateral LV free wall.

Echocardiography

Patients underwent quantitative echocardiography (GE-Vingmed Vivid 7, Horten, Norway) before and 6 months after CRT for digital analysis (GE EchoPac versions BT09-11). LV volumes and EF were calculated using a biplane Simpson’s rule and dimensions indexed.
to body surface area.\textsuperscript{8} Assessment for myocardial scar focused on the papillary muscle insertion sites using a wall motion score index where akinesis or dyskinesis and a reduction in end-diastolic wall thickness ≤0.6 cm were consistent with scar as suggested by the American Society of Echocardiography and European Association of Echocardiography.\textsuperscript{9} Specifically, the wall motion score index at the level of the papillary muscle attachment site was determined from the corresponding 8 LV segments as previously reported.\textsuperscript{10,11}

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>All Patients (N=277)</th>
<th>Patients With Follow-Up Echo (n=240)</th>
<th>Patients Without Significant MR After CRT (n=150)</th>
<th>Patients With Significant MR After CRT (n=90)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65±12</td>
<td>65±12</td>
<td>65±11</td>
<td>66±12</td>
<td>0.49</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>78 (28)</td>
<td>69 (29)</td>
<td>42 (28)</td>
<td>27 (30)</td>
<td>0.86</td>
</tr>
<tr>
<td>NYHA Class IV, n (%)</td>
<td>27 (10)</td>
<td>26 (11)</td>
<td>13 (9)</td>
<td>13 (14)</td>
<td>0.11</td>
</tr>
<tr>
<td>Heart failure type, n (%)</td>
<td>153 (55)</td>
<td>129 (54)</td>
<td>76 (51)</td>
<td>53 (59)</td>
<td>0.28</td>
</tr>
<tr>
<td>Ischemic</td>
<td>124 (45)</td>
<td>111 (46)</td>
<td>74 (49)</td>
<td>37 (41)</td>
<td></td>
</tr>
<tr>
<td>Nonischemic</td>
<td>147 (53)</td>
<td>131 (55)</td>
<td>83 (55)</td>
<td>48 (53)</td>
<td>0.99</td>
</tr>
<tr>
<td>QRS duration, mm</td>
<td>159±27</td>
<td>159±27</td>
<td>161±27</td>
<td>157±27</td>
<td>0.22</td>
</tr>
<tr>
<td>LBBB, n (%)</td>
<td>91 (33)</td>
<td>81 (34)</td>
<td>55 (37)</td>
<td>26 (29)</td>
<td>0.27</td>
</tr>
<tr>
<td>LVEDD, mm/m²</td>
<td>32±6</td>
<td>32±6</td>
<td>31±5</td>
<td>35±6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVESD, mm/m²</td>
<td>28±6</td>
<td>28±6</td>
<td>27±6</td>
<td>31±6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEDVI, mL/m²</td>
<td>102±38</td>
<td>101±38</td>
<td>94±34</td>
<td>113±43</td>
<td>0.0006</td>
</tr>
<tr>
<td>LVESVI, mL/m²</td>
<td>78±34</td>
<td>78±35</td>
<td>72±29</td>
<td>89±40</td>
<td>0.0005</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>24±6</td>
<td>24±6</td>
<td>25±6</td>
<td>23±6</td>
<td>0.0033</td>
</tr>
<tr>
<td>Baseline MR grade, n (%)</td>
<td>64 (23)</td>
<td>55 (23)</td>
<td>46 (31)</td>
<td>9 (10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No/trace</td>
<td>84 (30)</td>
<td>71 (30)</td>
<td>56 (37)</td>
<td>15 (17)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>82 (30)</td>
<td>73 (30)</td>
<td>39 (26)</td>
<td>34 (38)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>47 (17)</td>
<td>41 (17)</td>
<td>9 (6)</td>
<td>32 (35)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>40±25</td>
<td>39±24</td>
<td>41±22</td>
<td>36±27</td>
<td>0.16</td>
</tr>
<tr>
<td>Baseline IVMD, ms</td>
<td>93±37</td>
<td>92±37</td>
<td>93±35</td>
<td>89±41</td>
<td>0.36</td>
</tr>
<tr>
<td>Baseline OWD, ms</td>
<td>40±16</td>
<td>40±16</td>
<td>40±14</td>
<td>39±18</td>
<td>0.56</td>
</tr>
<tr>
<td>Baseline radial strain delay, ms</td>
<td>210±124</td>
<td>213±124</td>
<td>226±130</td>
<td>190±112</td>
<td>0.028</td>
</tr>
</tbody>
</table>

CRT indicates cardiac resynchronization therapy; IVMD, interventricular mechanical delay; LBBB, left bundle-branch block; LVEDDI, left ventricular end-diastolic diameter index; LVESDI, left ventricular end-systolic diameter index; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; MR, mitral regurgitation; NYHA, New York Heart Association; OWD, opposing wall delay; and SR, sinus rhythm. P values indicate statistical significance between patients with and without significant mitral regurgitation after CRT.
Quantification of MR Severity
Color Doppler quantification of MR was based on the guidelines of the American Society of Echocardiography and European Society of Cardiology using a multiparametric approach. A Nyquist limit of 40 to 60 cm/s and a color gain were used to optimize color Doppler jet visualization. Vena contracta width was measured as the narrowest portion of the MR color Doppler jet from zoomed optimized views. The ratio of the jet area to the left atrium area was measured by planimetry. Severity of MR was graded as mild with vena contracta width <0.3 cm and jet area <20%, moderate with vena contracta width 0.3 to 0.7 cm and jet area 20% to 40%, and severe with vena contracta width >0.7 cm and jet area >40%. The vena contracta width was considered the reference for MR severity if jet area values were discordant.

Speckle tracking radial strain was used from mid-LV short-axis images to assess radial dyssynchrony as previously described. Time to peak segmental radial strain was determined from onset of the QRS to the highest peak positive strain throughout the cycle with radial dyssynchrony defined as the time difference between the anteroseptal and posterior walls. Interobserver and intraobserver variability of echocardiographic analysis were as follows: 9±6% and 8±6% for EF, 4±1% and 3±1% for ESD, 11±7% and 7±6% for MR jet width, 9±6 and 8±6% for MR jet area, and 6±6% and 8±7% for radial dyssynchrony.

Follow-Up Echocardiography and Long-Term Outcome Assessment
Follow-up echocardiography was performed 6 months after CRT for assessment of MR severity and EF. EF response to CRT was defined as an absolute increase of LVEF ≥5% (EF units). The principal outcome variable was the combined end point of death, heart transplantation, or LV assist device (LV AD) implantation. This combined end point was predetermined because only patients with HF who are clinically considered end stage undergo transplantation or LVAD implantation at our institution.

Statistical Analysis
Continuous data are presented as the mean±SD and compared using the 2-tailed Student t test for independent samples and paired t tests for matched data, as appropriate. One-way analysis of variance has been used to test for differences across ≥2 groups. Frequencies of categorical variables were compared with the χ² test or Fisher exact test, as appropriate. Receiver-operator characteristic curve analysis was used to identify the cutoff for continuous variables predicting amelioration of significant MR after CRT, selecting the cutoff value yielding the highest sum of specificity and sensitivity. Univariable and multivariable logistic regression were applied to evaluate independent correlates of improvement in MR after CRT. A stepwise procedure used a combination of forward selection and backward elimination where at each forward step of adding a new variable, the model was re-evaluated, and variables losing significance were eliminated. Cutoff value of P<0.05 was used for the entry step, and cutoff of P<0.1 was used for the retention step. The odds ratio and the 95% confidence intervals (CI) were calculated for the parameters estimated in the regression model. The Kaplan–Meier method was used to estimate the probability of event-free survival, and log-rank test was applied to test the equivalence of survival curves. A Cox proportional hazard regression model was used to assess the significance of response to CRT and MR reduction using the echocardiographic feature scoring system and its association with long-term outcome, with adjustment for baseline variables. Statistical significance was defined as P<0.05.

Results
Of the 302 consecutive patients with HF referred for CRT, 23 (8%) patients were excluded because of echocardiographic image quality unsuitable for quantitative analysis, and 2 patients were excluded because of a prosthetic mitral valve. Accordingly, 277 patients were included with complete baseline data. Their age was 65±12 years, 78 (28%) were female, LVEF was 24±6%, and 153 (55%)
patients had ischemic disease. At baseline, MR was absent in 64 (23%) patients, mild in 84 (30%), moderate in 82 (30%), and severe in 47 (17%) patients. Significant MR (≥moderate) was present in 129 patients (47%) at baseline. Optimal medical therapy was achieved in >85% of patients tolerating angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and β-blockers. All CRT devices were programmed to simultaneous biventricular pacing. Baseline characteristics between patients with and without significant MR after CRT were similar except for those with significant MR after CRT who had more dilated LVs and lower EFs at baseline (Table 1).

Association of MR After CRT With Long-Term Outcome

Follow-up echocardiography was performed on 240 patients; 8 died, 2 were transplanted and 27 patients did not return for imaging, although follow-up clinical data were available. Of the 114 patients with significant baseline MR and follow-up echocardiography, 48 (42%) improved to mild or no MR, 42 (37%) had no change in MR, and 24 (21%) patients had MR worsening. Of the 126 patients without significant MR at baseline, 24 (19%) had newly developed significant MR: 16 with moderate and 8 patients with severe MR. When combined, 90 patients (38% of total) had significant MR after CRT.

During a follow-up of 4 years, 66 unfavorable events occurred; 47 patients died, 10 underwent heart transplantation, and 9 required LVAD implantation. Interestingly, the finding of significant MR before CRT was not associated with long-term event-free survival (Figure 2A). However, patients with significant MR after CRT, independent of pre-CRT MR, had a comparatively less favorable event-free survival (hazard ratio, 3.58; 95% CI, 2.18–5.87; \( P < 0.0001 \); Figure 2B). Furthermore, the degree of MR after CRT was inversely associated with event-free survival. In other words, patients with the greatest degree of MR had the least favorable outcome (\( P < 0.0001 \); Figure 2C). Patients with newly developed significant MR after CRT had a similar unfavorable event-free survival as those the patients with persistent significant MR after CRT. Overall, there were 126 of 224 patients (56%) with an EF response after CRT defined as ≥5% increase in absolute EF units, which was associated with a more favorable long-term outcome (hazard ratio, 0.54; 95% CI, 0.32–0.91; \( P = 0.02 \) (Figure 3A). When MR and EF response were considered together, significant differences in long-term outcome among subgroups were observed (\( P < 0.0001 \)). Regardless of EF response, patients with

![Figure 3](http://circheartfailure.ahajournals.org/)

Figure 3. Mitral regurgitation (MR), ejection fraction (EF) response, and long-term outcome. Kaplan–Meier curves of probability of survival free from transplantation, or left ventricular assist device after cardiac resynchronization therapy (CRT). A, Patients stratified by EF response defined as an absolute increase in EF by 5% (EF units), showing more favorable outcomes in patients with EF a positive response (+). B, Patients stratified by both EF response and presence of significant MR (+) or absence of significant MR (−) after CRT. MR after CRT was more closely associated with event-free survival than EF response alone.
significant MR after CRT had a less favorable outcome than those without significant MR (P<0.0001 and P=0.002, respectively; Figure 3B).

Factors Associated With Improvement in MR After CRT
Of the 114 patients with moderate or severe MR at baseline, 48 (42%) improved to mild or no MR after CRT; specifically, 17 (15%) patients had mild MR, and 31 (27%) patients had no MR on follow-up echocardiography. A univariable logistic regression model was first tested for associations of improvement in MR after CRT in 17 baseline characteristics in Table 1. LV end-diastolic diameter index, LV end-systolic diameter index, baseline MR grade, baseline radial dyssynchrony, and lack of scar at papillary muscle site were factors associated with MR reduction (Table 2; Figure 4). Using receiver-operator characteristic curve analysis and a multivariable logistic stepwise model, the following characteristics were independently associated with improvement in MR after CRT: radial dyssynchrony >200 ms (P=0.028), LV end-systolic diameter index <29 mm/m² (P=0.042), and lack of wall motion consistent with scar at papillary muscle insertion sites assessed by wall motion score index ≤2.5 (P=0.036; Table 3).

We tested the additive value of these 3 echocardiographic features associated with MR reduction after CRT by devising a simple scoring system, which assigned 1 point for each. Logistic analysis demonstrated that this scoring system was associated with improvement in MR after CRT (odds ratio, 0.20; 95% CI, 0.11–0.39; P<0.0001). The patients with higher MR reduction scores also had significant improvements in LV end-systolic volume and LVEF after CRT (Figure 5). Moreover, this MR reduction score was significantly associated with the long-term survival after CRT (hazard ratio, 0.32, 95% CI, 0.18–0.57, P=0.0001; Figure 6). The 28 patients with all 3 of these baseline features associated with MR reduction had the most favorable long-term survival, followed by the 48 patients with 2 features. The 38 patients who had an MR reduction score of either 0 or 1 had the least favorable long-term survival.

Twenty-four of the 126 patients (19%) that started with none or mild MR worsened to significant MR when observed 6 months after CRT. These patients with newly developed significant MR after CRT had a similar unfavorable outcome as those the patients with persistent significant MR after CRT. Using a similar multivariable statistical approach to examine the same 17 clinical and echocardiographic variables above, patients with newly developed MR after CRT were more likely to a dilated LV end-diastolic diameter index (P=0.003) and have atrial fibrillation with atrioventricular node ablation (P=0.04). Although this subgroup is too small to reach a definite conclusion, these observations suggest that progression of MR may be related to the disease process and myocardial substrate in these patients receiving CRT.

Table 2. Univariable Logistic Analyses for Prediction of Improvement in Mitral Regurgitation After CRT

<table>
<thead>
<tr>
<th>Variables</th>
<th>Improved to Insignificant MR (n=48)</th>
<th>Persistent Significant MR (n=66)</th>
<th>PValue</th>
<th>OR</th>
<th>95% CI</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65±13</td>
<td>68±11</td>
<td>0.378</td>
<td>0.98</td>
<td>0.95–1.014</td>
<td>0.26</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>16 (33)</td>
<td>20 (30)</td>
<td>0.89</td>
<td>1.15</td>
<td>0.52–2.55</td>
<td>0.73</td>
</tr>
<tr>
<td>Ischemic pathogenesis, n (%)</td>
<td>24 (50)</td>
<td>40 (61)</td>
<td>0.35</td>
<td>0.65</td>
<td>0.31–1.38</td>
<td>0.26</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>5 (10)</td>
<td>12 (18)</td>
<td>0.38</td>
<td>0.52</td>
<td>0.17–1.59</td>
<td>0.24</td>
</tr>
<tr>
<td>LBBB, n (%)</td>
<td>30 (63)</td>
<td>33 (50)</td>
<td>0.29</td>
<td>1.62</td>
<td>0.75–3.46</td>
<td>0.21</td>
</tr>
<tr>
<td>QRS duration, mm</td>
<td>165±30</td>
<td>156±27</td>
<td>0.10</td>
<td>1.01</td>
<td>0.99–1.02</td>
<td>0.10</td>
</tr>
<tr>
<td>LVEDDI, mm/m²</td>
<td>31±5</td>
<td>35±6</td>
<td>0.012</td>
<td>0.93</td>
<td>0.86–0.99</td>
<td>0.031</td>
</tr>
<tr>
<td>LVESDI, mm/m²</td>
<td>27±5</td>
<td>31±6</td>
<td>0.0051</td>
<td>0.92</td>
<td>0.85–0.99</td>
<td>0.013</td>
</tr>
<tr>
<td>LVEDV, mL/m²</td>
<td>98±38</td>
<td>113±44</td>
<td>0.060</td>
<td>0.99</td>
<td>0.98–1.001</td>
<td>0.052</td>
</tr>
<tr>
<td>LVESV, mL/m²</td>
<td>76±33</td>
<td>89±41</td>
<td>0.064</td>
<td>0.99</td>
<td>0.98–1.001</td>
<td>0.055</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>24±6</td>
<td>22±6</td>
<td>0.17</td>
<td>1.05</td>
<td>0.98–1.12</td>
<td>0.16</td>
</tr>
<tr>
<td>Baseline MR grade, n (%)</td>
<td>Moderate/severe 39/81 (9/19)</td>
<td>34 (52)/32 (48)</td>
<td>0.0022</td>
<td>0.25</td>
<td>0.10–0.59</td>
<td>0.0016</td>
</tr>
<tr>
<td>Papillary muscle site scar (WMSI)</td>
<td>2.01</td>
<td>2.55</td>
<td>0.0001</td>
<td>0.28</td>
<td>0.14–0.55</td>
<td>0.0001</td>
</tr>
<tr>
<td>IVMD, ms</td>
<td>40±20</td>
<td>36±25</td>
<td>0.34</td>
<td>1.0087</td>
<td>0.99–1.03</td>
<td>0.34</td>
</tr>
<tr>
<td>OWD, ms</td>
<td>92±33</td>
<td>91±38</td>
<td>0.89</td>
<td>1.0008</td>
<td>0.98–1.01</td>
<td>0.89</td>
</tr>
<tr>
<td>Yu index, ms</td>
<td>40±15</td>
<td>40±17</td>
<td>0.85</td>
<td>0.9976</td>
<td>0.97–1.02</td>
<td>0.85</td>
</tr>
<tr>
<td>Radial dyssynchrony, ms</td>
<td>254±118</td>
<td>198±114</td>
<td>0.013</td>
<td>1.0042</td>
<td>1.001–1.008</td>
<td>0.013</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; CRT, cardiac resynchronization therapy; IVMD, interventricular mechanical delay; LBBB, left bundle-branch block; LVEDDI, left ventricular end-diastolic diameter index; LVEDV, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESDI, left ventricular end-systolic diameter index; LVESV, left ventricular end-systolic volume index; MR, mitral regurgitation; OWD, opposing wall delay; OR, odds ratio; and WMSI, wall motion score index.

Discussion
This present study in a large series of patients with HF with routine CRT indications demonstrated that MR is an important common finding, and that reduction in significant MR after CRT is variable. Approximately one third of patients had significant MR after CRT, which was strongly associated with a less favorable long-term event-free survival than their...
counterparts who had mild or no MR after CRT. Furthermore, the degree of MR after CRT was closely associated with outcome, and the MR response seemed to be of more important prognostic significance than EF response alone. This report extends existing literature by demonstrating the following 3 mechanistic echocardiographic features observed to be strongly associated with amelioration of significant MR after CRT: presence of radial dyssynchrony before CRT, absence of excessive LV dilatation, and absence of echocardiographic evidence of scar at the papillary muscle insertion site. Patients with newly developed or persistent significant MR after CRT had a similarly less favorable outcome having prognostic importance to patients with CRT.

Impact of Significant MR After CRT on Long-Term Outcome
This study supports previous observations that MR after CRT portends a poor prognosis.18–20 van Bommel et al18 reported in 98 consecutive patients with CRT with moderate-severe MR that a reduction of ≥1 grades at 6 months was independently associated with improved survival (hazard ratio; 0.35, 95% CI, 0.13–0.94; P<0.043). Verhaert et al19 also recently

<table>
<thead>
<tr>
<th>Variables</th>
<th>Coefficient</th>
<th>SE</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial dyssynchrony &gt;200 ms</td>
<td>0.97</td>
<td>0.44</td>
<td>2.65</td>
<td>1.11–6.30</td>
<td>0.0277</td>
</tr>
<tr>
<td>End-systolic diameter index &lt;29 mm/m²</td>
<td>0.93</td>
<td>0.46</td>
<td>2.53</td>
<td>1.03–6.20</td>
<td>0.0420</td>
</tr>
<tr>
<td>Papillary muscle site (WMSI) ≤2.5</td>
<td>0.95</td>
<td>0.45</td>
<td>2.59</td>
<td>1.06–6.30</td>
<td>0.0360</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; OR, odds ratio; and WMSI, wall motion score index.
reported in 266 consecutive patients with CRT that MR reduction was associated with a favorable impact on death, transplantation, or LV AD ($P < 0.0001$). Although EF response is associated with favorable outcomes after CRT, our study demonstrated that improvement in MR seemed to confer a more favorable association with long-term outcome than EF response alone. van Bommel et al$^{18}$ similarly reported that MR reduction independently of end-systolic volume response was predictive of favorable CRT response. This may be expected because of the unloading effect of significant MR, which affects EF as a measure of LV function.

**Mechanisms of Improvement in MR After CRT**

Decreases in MR after CRT have been attributed to a complex interaction of mechanisms, including recoringodation of the papillary muscle closing forces,$^{20,23,24}$ reductions in LV volumes with decreases in mitral leaflet tenting angles, and augmentation of transmitral pressure gradient attributable to increased contractility.$^{22,25,26}$ Breithardt et al showed that reduction in MR immediately after CRT was directly related to the increase in ($r = -0.83; P < 0.0001$).$^{27}$ We previously correlated reductions in MR after CRT with resynchronized timing of the papillary muscle contraction using longitudinal strain imaging ($r = 0.77; P < 0.001$).$^{28}$ Because the degree of baseline dyssynchrony before CRT was variable, we related reductions in MR to reductions in dyssynchrony in our present study. Ypenburg et al$^{28}$ also related improvements in significant MR after CRT to baseline radial dyssynchrony. More recently, Solis et al$^{29}$ related timing of papillary muscle contraction to improvements in closing forces on the mitral valve and increases in dP/dt.

LV dilatation is a major contributor to functional MR in patients with HF,$^{30}$ and improvement in MR is strongly associated with reverse remodeling, decreases in LV volumes, and more favorable outcome after CRT.$^{31-34}$ Liang et al$^{35}$ related an 11% decrease in MR volume with LV reverse remodeling after CRT. Solis et al$^{29}$ also observed beneficial LV geometric and volumetric changes after CRT from reverse remodeling, affecting mitral valve annular area, leaflet closing area, and tenting volume ($P < 0.001$). Our present study extends these observations that excessive LV dilatation at baseline, simply measured by end-systolic diameter index, was associated with lack of improvement in MR after CRT. We hypothesize that there may be a limit to LV dilatation that is reversible by CRT, and excessive LV dilatation may be a marker for lack of improvement in MR and nonresponse to CRT, and may be associated with the development of new MR after CRT. Finally, Levine et al were among the first to relate the mechanism of MR to ischemia or infarction of the papillary muscle or adjacent insertion site, causing retraction of the chordae tendineae and incomplete leaflet coaptation.$^{20}$ Hung et al$^{36}$ used an animal model to demonstrate that scar at the site of the papillary muscle insertion was directly related to ischemic MR, and that repositioning of the papillary muscle may reduce MR without compromising LV function. Other factors related to MR and unfavorable outcome in patients with CRT include
global scar burden,\textsuperscript{5,7} and scar at the site of the LV lead \textsuperscript{6,38,39} which may be related to scar at the papillary muscle insertion sites. Our present study combines the important elements of baseline dyssynchrony, lack of excessive LV dilatation, and lack of scar at the papillary muscle insertion site as factors that are independently associated with improvements in MR, and combine them in a unique scoring system.

**Study Limitations**

A limitation was that the MR reduction score was developed in a relatively small number of patients, and we emphasize that this echocardiographic feature scoring system needs to be tested prospectively in a larger series of patients with CRT to determine its true predictive value. Furthermore, because of a small sample size and the large number of characteristics tested, there is a chance of false-positive findings. The clinical relevance of both the composite MR score and the individual components of the MR score need to be validated in further studies. Another limitation was that MR severity was quantified by color Doppler vena contracta width and jet area/left atrial ratio, and not by proximal isovelocity surface area. However, all methods to assess MR have limitations. Our approach of selecting maximal vena contracta width may be considered a more direct and simple means to estimate orifice area. Recent 3-dimensional Doppler investigations suggest that the regurgitant orifice area is often elliptical and not circular.\textsuperscript{40} Importantly, MR severity by our methods translated to clinically relevant patient outcomes after CRT. Another limitation was that measurement of dyssynchrony by speckle tracking echocardiography requires technically adequate image quality, and operator experience. Finally, it may be considered a limitation that other clinical assessments like changes in New York Heart Association functional class or 6-minute walk distance were not part of this study. However, we choose to focus on the important objective end points of death, heart transplant, or LVAD.

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**CLINICAL PERSPECTIVE**

Cardiac resynchronization therapy (CRT) is an important therapy for patients with heart failure with widened QRS and depressed ejection fraction. Patients with more than mild mitral regurgitation (MR) after CRT have a comparative unfavorable outcome. Because mechanisms of MR reduction with CRT are complex, this investigation on 277 patients who underwent CRT identified 3 echocardiographic features that were observed to be independently associated with amelioration of significant MR after CRT by multivariable analysis. The features were the following: anterosertal to posterior wall radial strain dyssynchrony >200 ms, lack of severe left ventricular dilatation (end-systolic dimension index <29 mm/m²), and lack of echocardiographic scar at papillary muscle insertion sites (all P<0.05). When combined by a simple scoring system, they were additively predictive of reduction in MR, which was associated with improved long-term survival (P=0.0001) after CRT. Although these features need to be tested prospectively to ascertain their true predictive value, these observations provide practical information, which may help the clinician understand CRT outcomes in patients with MR.
Mechanistic Features Associated With Improvement in Mitral Regurgitation After Cardiac Resynchronization Therapy and Their Relation to Long-Term Patient Outcome
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