Cardiac Resynchronization Therapy as a Therapeutic Option in Patients With Moderate-Severe Functional Mitral Regurgitation and High Operative Risk

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Introduction—Functional mitral regurgitation (MR) is a common finding in heart failure patients with dilated cardiomyopathy and has important prognostic implications. However, the increased operative risk of these patients may result in low referral or high denial rate for mitral valve surgery. Cardiac resynchronization therapy (CRT) has been shown to have a favorable effect on MR. Aims of this study were to (1) evaluate CRT as a therapeutic option in heart failure patients with functional MR and high operative risk and (2) investigate the effect of MR improvement after CRT on prognosis.

Methods and Results—A total of 98 consecutive patients with moderate-severe functional MR and high operative risk underwent CRT according to current guidelines. Echocardiography was performed at baseline and 6-month follow-up; severity of MR was graded according to a multiparametric approach. Significant improvement of MR was defined as a reduction ≥1 grade. All-cause mortality was assessed during follow-up (median 32 [range 6.0 to 116] months). Thirteen patients (13%) died before 6-months follow-up. In the remaining 85 patients, significant reduction in MR was observed in all evaluated parameters. In particular, 42 patients (49%) improved ≥1 grade of MR and were considered MR improvers. Survival was superior in MR improvers compared to MR nonimprovers (log rank P<0.001). Mitral regurgitation improvement was an independent prognostic factor for survival (hazard ratio 0.35, confidence interval 0.13 to 0.94; P=0.043).

Conclusions—Cardiac resynchronization therapy is a potential therapeutic option in heart failure patients with moderate-severe functional MR and high risk for surgery. Improvement in MR results in superior survival after CRT. (Circulation. 2011;124:00-00.)

Key Words: biventricular pacing ■ cardiac resynchronization therapy ■ mitral regurgitation ■ prognosis

Functional mitral regurgitation (MR) is a common finding in heart failure patients with ischemic or nonischemic dilated cardiomyopathy.1,2 More importantly, the presence of MR has important prognostic implications in these patients.1,3 The initial strategy of treating MR is optimization of medical therapy (afterload reduction and treatment of fluid load). However, in many patients significant functional MR persists and surgery may be the final option to reduce the extent of MR. The main surgical technique for treatment of functional MR is restrictive annuloplasty, with or without additional surgical left ventricular (LV) remodeling. In many of the patients, however, the increased operative mortality risk may result in either a low referral or high denial rate for mitral valve surgery. A recent study by Bach et al reported a nonreferral or denial rate for surgery as high as 84% in patients with moderate-to-severe or severe functional MR.4 Moreover, it is currently unclear whether mitral valve surgery improves prognosis in this specific group of patients.5 As a result, indications for mitral valve surgery in heart failure patients with functional MR are not well defined by any currently available guideline.6

Clinical Perspective on p ●●●

Conversely, cardiac resynchronization therapy (CRT) has been shown to have a favorable effect on functional MR. There are several studies that have demonstrated a reduction in extent of functional MR after CRT.7–12 Most of these studies, however, were performed in patients with only mild-moderate MR, and therefore less is known about the effects of CRT in patients with moderate-severe functional MR. Furthermore, these studies were limited to changes at midterm (6 months) follow-up, and therefore no data exist with regard to the potential beneficial effects of reduction in MR on long-term prognosis. Consequently, the aims of this
study were (1) to evaluate the role of CRT as an alternative therapeutic option in heart failure patients with moderate-severe functional MR and high operative risk and (2) to investigate the effect of reduction in severity of MR after CRT on long-term prognosis.

Methods

Patient Population and Data Collection
A total of 98 consecutive patients with moderate-severe functional MR and high operative risk were included. These patients are part of an ongoing registry and were referred for CRT according to the current guidelines. Patient data were prospectively collected in the departmental Cardiology Information System (EPD-Vision, Leiden University Medical Center, Leiden, the Netherlands).

Cause of heart failure was considered ischemic in the presence of significant coronary artery disease (≥50% stenosis in ≥1 of the major coronary arteries) and/or a history of myocardial infarction or prior revascularization. The protocol was as follows: In all patients, clinical status was assessed before implantation and at 6 months follow-up. Extensive echocardiography was performed at baseline and repeated 6 months after CRT to (1) quantify LV volumes and function and (2) evaluate the severity of MR. After the 6-month follow-up, patients were scheduled for regular visits to the outpatient clinic.

Clinical Evaluation
In all patients, evaluation of heart failure symptoms according to the New York Heart Association (NYHA) classification was performed. Assessment of quality of life was performed using the Minnesota Living with Heart Failure Questionnaire (high scores indicating poor quality of life), and when possible exercise capacity was measured using the 6-minute walk test. In addition, operative risk was assessed by means of the logistic Euroscore. Estimated glomerular filtration rate (eGFR) was calculated using the standard formula by Cockcroft and Gault and expressed in mL.min⁻¹.1.73 m⁻². Finally, outcome data were collected by chart review, device interrogation, and telephone contact. Primary end point during long-term follow-up was death from any cause.

Echocardiography
All patients underwent echocardiography in the left lateral decubitus position before and 6 months after CRT implantation. Imaging was performed using a commercially available echocardiographic system (VIVID 7, General Electric Vingmed Ultrasound, Milwaukee, WI). Images were obtained using a 3.5 MHz transducer at a depth of 16 cm in the parasternal and apical (2-, 3-, and 4-chamber) views. All images were recorded digitally in cine-loop format and analyzed offline with commercial software (EchoPac 108.1.5, General Electric Vingmed Ultrasound).

Left Ventricular Volumes and Function Analysis
LV end-diastolic and LV end-systolic volumes (LVEDV and LVESV, respectively) were determined from the conventional apical 2- and 4-chamber views, and LV ejection fraction (LVEF) was calculated using the biplane Simpson technique. Volumetric response to CRT was defined as a reduction ≥15% in LVESV at 6 months follow-up.

Assessment of Mitral Regurgitation Severity
Following current guidelines, we assessed the severity of MR using a multiparametric approach, which combined the following measurements: (1) vena contracta width (VCW), measured as the narrowest portion of the MR color Doppler jet in a zoomed optimized parasternal long-axis view or in the apical 4-chamber view; (2) the ratio of the jet area to the left atrium (LA) area measured by planimetry in the 4-chamber view; (3) the effective regurgitant orifice area (EROA) calculated with the proximal isovelocity surface area method. The color Doppler images were acquired using a Nyquist limit of 30 to 60 cm/s and a color gain that just eliminates random color speckle from nonmoving regions. Severity of MR was defined using a multiparametric approach according to current guidelines and graded on a 4-point scale: mild (EROA < 0.2 cm²), moderate (0.2 ≤ EROA < 0.7 cm²), moderate-severe (0.7 ≤ EROA < 1.5 cm²), and severe (EROA ≥ 1.5 cm²). Improvement in MR was defined as a reduction ≥1 grade 6 months after CRT. In addition, as a measure of mitral valve deformation, valvular tenting area was measured from the parasternal long-axis view at mid-systole as the area enclosed between the annular plane and mitral leaflets. Left atrium volumes were measured form the 2- and 4-chamber views using the biplane Simpson technique. Finally, estimated systolic pulmonary artery pressure (SPAP) was derived from the right ventricular to right atrial pressure gradient or tricuspid regurgitant jet gradient and calculated with the modified Bernoulli equation.

Statistical Analysis
Continuous data are presented as mean±SD, and dichotomous data are presented as n (%). Comparison of data at baseline and 6-month follow-up was performed with the paired-samples t test. Comparison of data between patient groups was performed using the independent-samples t test for continuous data. The Fisher exact tests or χ² tests were used as appropriate to compare dichotomous data. Analysis of variance for repeated measurements, including interaction between group and time, was applied for comparison of data between patient groups at baseline and 6 months follow-up. The event-free survival of patients was evaluated with the Kaplan–Meier method and the log rank test. The effect of improvement in MR on event-free survival, adjusted for other variables, was investigated using the Cox proportional hazards model. Variables that showed a
statistically significant effect in the univariate analyses were entered in the multivariate Cox proportional hazards model. The proportional hazards assumption was checked for continuous variables by visual inspection of scaled Schoenfeld residuals and for categorical variables by visual inspection of log-log plots. All analyses were performed with SPSS for Windows, version 16.0 (SPSS, Chicago, IL). All statistical tests were 2-sided. A P value < 0.05 was considered statistically significant.

Results

Patient Characteristics

Baseline characteristics of the patient population are presented in Table 1. The majority of patients were men (74%), and the underlying cause of heart failure was ischemic cardiomyopathy in 62 patients (63%). All patients had moderate-severe MR (63% grade 3 and 37% grade 4) with a central jet secondary to significant LV dilatation and dysfunction. Furthermore, all patients were characterized by a high operative risk (logistic Euroscore 26 ± 13%, mean eGFR 51 ± 22 mL min⁻¹ 1.73 m²⁻¹, diabetes mellitus in 19% of cases). Optimal medical therapy was administered to all patients, if tolerated. Implantation of a CRT device was successful in all patients, and no procedure-related complications were observed. All devices were programmed to simultaneous biventricular pacing during the first 6 months of follow-up. Before the 6-month follow-up, 13 patients died (10 patients died because of heart failure, 2 patients died because of severe infection, and 1 patient died because of a malignancy). Therefore, further analysis (baseline versus follow-up) was performed in the remaining 85 patients. Of note, patients who died before the 6-month follow-up had a higher logistic Euroscore (34 ± 15 versus 24 ± 12), lower eGFR (40 ± 15 mL min⁻¹ 1.73 m²⁻¹ versus 53 ± 23 mL min⁻¹ 1.73 m²⁻¹) and were in a higher NYHA class (3.4 ± 0.5 versus 3.1 ± 0.3) at baseline compared with patients who survived the first 6 months of follow-up.

Clinical and Left Ventricular Functional Changes After 6 Months of Cardiac Resynchronization Therapy

At 6-month follow-up, the mean NYHA class improved from 3.1 ± 0.3 to 2.1 ± 0.7 (P < 0.001). In addition, the quality of life score decreased from 38 ± 18 to 24 ± 17 (P < 0.001) whereas distance covered in the 6-minute walk test increased from 283 ± 109 m to 368 ± 120 m (P < 0.001). Significant LV reverse remodeling was observed at 6-month follow-up, as shown by a decrease in LVEDV from 261 ± 88 mL at baseline to 233 ± 81 mL at follow-up and a decrease in LVESV from 205 ± 81 mL to 166 ± 72 mL (both P < 0.001). Furthermore, an increase in LVEF from 23 ± 7% at baseline to 30 ± 9% at follow-up was noted (P < 0.001). Volumetric response to CRT (reduction ≥ 15% in LVESV at 6-month follow-up) was observed in 54 patients (55%).

Changes in Mitral Regurgitation Severity After 6 Months of Cardiac Resynchronization Therapy

Severity of MR improved significantly according to all evaluated parameters (Figure 1). The VCW decreased from

![Figure 1. Changes in severity of MR at 6-month follow-up. Improvement in severity of MR at 6 months follow-up was observed in all evaluated parameters (A, VCW; B, EROA; C, tenting area; D, LA volume; E, Jet area/LA area; F, SPAP). Error bars represent standard deviation. VCW indicates vena contracta width; EROA, effective regurgitant orifice area; LA, left atrium; and SPAP, systolic pulmonary artery pressure.](image-url)
0.74±0.15 cm at baseline to 0.59±0.21 cm at follow-up ($P<0.001$) whereas the EROA decreased from 0.51±0.16 cm$^2$ to 0.43±0.18 cm$^2$ ($P=0.001$). Tenting area decreased from 7.2±2.0 cm$^2$ at baseline to 6.2±2.0 cm$^2$ at follow-up ($P<0.001$), and the LA volume decreased from 103±38 mL to 91±32 mL ($P<0.001$). Finally, the regurgitant jet area ratio decreased from 51±14% at baseline to 41±18% at follow-up ($P<0.001$) and mean SPAP decreased from 35±10 mm Hg to 31±10 mm Hg ($P=0.001$). An example of significant improvement in severity of MR is displayed in Figure 2.

Mitral Regurgitation Improvers Versus Mitral Regurgitation Nonimprovers After Cardiac Resynchronization Therapy

At 6-month follow-up, MR improvement (reduction ≥1 grade of MR as previously described) was noted in 42 patients (49%). These patients were therefore considered MR improvers. Baseline clinical characteristics were comparable between MR improvers and MR nonimprovers. However, ischemic cause of heart failure was more frequently observed among MR nonimprovers (Table 2). In addition, MR improvers had slightly less symptomatic heart failure (according to the NYHA functional class).

Comparison of clinical and echocardiographic data between MR improvers and nonimprovers, both at baseline and 6-month follow-up, is displayed in Table 3. At 6-month follow-up, both MR improvers and MR nonimprovers had an improvement in clinical characteristics. However, these improvements were more pronounced in MR improvers. All baseline echocardiographic parameters were comparable between MR improvers and nonimprovers. At 6-month follow-up, reductions in LV volumes and an increase in LVEF were observed in both groups. Of note, 39 MR improvers (93%) also had significant LV volumetric response, versus only 15 patients (35%) in the MR nonimprovers group ($P<0.001$). By definition, MR improvers had a significant decrease in MR severity.

**Figure 2.** Example of a patient with a significant improvement in MR at 6-month follow-up. At baseline, the MR jet area exceeded 80% of the LA area, and the EROA was 0.61 cm$^2$. A, Four-chamber view; B, parasternal long-axis view. At 6-month follow-up, the jet area decreased to 10% of the LA area and the EROA was 0.19 cm$^2$. C, Four-chamber view; D, parasternal long-axis view.

<table>
<thead>
<tr>
<th>Variable</th>
<th>MR Improvers (n=42)</th>
<th>MR Nonimprovers (n=43)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70±8</td>
<td>70±7</td>
<td>0.914</td>
</tr>
<tr>
<td>Men/Women, n/n</td>
<td>28/14</td>
<td>34/9</td>
<td>0.229</td>
</tr>
<tr>
<td>Cause of heart failure, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>20 (48)</td>
<td>32 (74)</td>
<td>0.015</td>
</tr>
<tr>
<td>Nonischemic</td>
<td>22 (52)</td>
<td>11 (26)</td>
<td></td>
</tr>
<tr>
<td>eGFR, mL·min$^{-1}$·1.73 m$^{-2}$</td>
<td>55±23</td>
<td>51±23</td>
<td>0.432</td>
</tr>
<tr>
<td>Diabetes mellitus, n</td>
<td>5 (12)</td>
<td>10 (23)</td>
<td>0.255</td>
</tr>
<tr>
<td>Medication, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>40 (95)</td>
<td>41 (95)</td>
<td>0.981</td>
</tr>
<tr>
<td>Diuretics</td>
<td>38 (90)</td>
<td>39 (91)</td>
<td>0.972</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>35 (83)</td>
<td>38 (88)</td>
<td>0.505</td>
</tr>
<tr>
<td>$\beta$-blockers</td>
<td>25 (60)</td>
<td>25 (58)</td>
<td>0.897</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>20 (48)</td>
<td>24 (56)</td>
<td>0.450</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean±SD.

MR indicates mitral regurgitation; eGFR, estimated glomerular filtration rate; and ACE, angiotensin-converting enzyme.
grade from 3.3±0.5 to 1.8±0.6, and this was evidenced by significant improvement in all evaluated parameters. Conversely, MR nonimprovers showed (by definition) no improvement in MR grade from 3.3±0.5 to 3.4±0.6.

**Table 3. Changes in Clinical and Echocardiographic Characteristics of MR Improvers and Nonimprovers at 6-Month Follow-Up**

<table>
<thead>
<tr>
<th>Variable</th>
<th>MR Improvers (n=42)</th>
<th>MR Nonimprovers (n=43)</th>
<th>P</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-Up</td>
<td></td>
<td>Group and Time</td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.0±0.2</td>
<td>1.9±0.7‡</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>6 MWT, m</td>
<td>299±113</td>
<td>407±121*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QoL score</td>
<td>35±17</td>
<td>19±16*</td>
<td>0.117</td>
<td></td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td>255±84</td>
<td>214±78‡</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>LVESV, mL</td>
<td>201±80</td>
<td>146±69‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
<td>23±7</td>
<td>33±10†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VCW, cm</td>
<td>0.73±0.14</td>
<td>0.44±0.16†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EROA, cm²</td>
<td>0.51±0.16</td>
<td>0.31±0.12†</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>TA, cm²</td>
<td>7.1±2.1</td>
<td>5.5±1.7‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jet area/LA area, %</td>
<td>51±14</td>
<td>29±15*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPAP, mm Hg</td>
<td>34±10</td>
<td>25±6*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MR grade</td>
<td>3.3±0.5</td>
<td>1.8±0.6*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MR indicates mitral regurgitation; NYHA, New York Heart Association; 6 MWT, 6-minute walk test; QoL, quality of life; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; VCW, vena contracta width; EROA, effective regurgitant orifice area; TA, tenting area; LA, left atrium; and SPAP, systolic pulmonary artery pressure. *P<0.05, baseline vs follow-up; †P=0.001, baseline vs follow-up; ‡P<0.001, baseline vs follow-up.

**Discussion**

The findings of the present study can be summarized as follows: (1) CRT reduces severity of MR at 6-month follow-up in heart failure patients with moderate-severe functional MR and at high risk for mitral valve surgery, and (2) improvement in MR results in superior survival during long-term follow-up.

**Functional Mitral Regurgitation in Heart Failure**

In heart failure patients with impaired LV systolic function, MR is a frequent finding. It is estimated that nearly half of these patients have some degree of MR, and in ≈30% of these cases, extent of MR can be graded as moderate or severe. In most patients, a structurally normal mitral...
Effects of Cardiac Resynchronization Therapy on Functional Mitral Regurgitation

Contrasting with the above-mentioned results on surgery for functional MR, previous studies on the effects of CRT have not only demonstrated improved survival but also a significant reduction in extent of functional MR after CRT. Most of the studies on changes in MR after CRT were single-center studies with limited numbers of patients. Nonetheless, results among these studies are consistent, and several explanations for improvement in MR, including the immediate effect of resynchronization and improvement of LV contraction (inducing synchronized mechanical activation of papillary muscle insertion sites), and the more delayed effect of favorable changes in mitral valve geometry (LV reverse remodeling) have been proposed. Moreover, in the Cardiac Resynchronisation in Heart Failure (CARE-HF) trial, which randomized 813 patients to receive either biventricular pacing in addition to optimized medical therapy or optimized medical therapy alone, there was a significantly greater reduction in MR (measured by the regurgitant jet area ratio) in patients who received CRT compared with patients on optimized medical therapy alone 3 months after CRT (difference in means 5.1%, P<0.001). Finally, pooled data from several major studies including 357 patients implanted with a CRT device, with a follow-up of at least 6 months, showed a reduction in functional MR (measured by the regurgitant jet area) of 30% to 40% after CRT. The above-mentioned results clearly demonstrate the beneficial effects of CRT on functional MR.

Several contributing factors to nonresponse to CRT, such as inappropriate LV lead positioning and, in patients with ischemic cardiomyopathy, the extent and location of scar tissue, have been previously reported. These factors might also have a significant effect on the changes in MR after CRT. Positioning the LV pacing lead at the optimal site (latest activated myocardial segment) may improve MR during CRT by any of the 2 mechanisms described above (synchronized mechanical activation of papillary muscle insertion sites and LV reverse remodeling during follow-up). Conversely, the presence of significant scar tissue may limit the extent of LV reverse remodeling after CRT and therefore also prevent the improvement in MR. In addition, positioning the LV lead at the level of a nonviable myocardial segment may significantly hamper the beneficial effect of CRT on LV remodeling and MR. Specific studies are needed to further explore the relationship between these different factors and the improvement of MR after CRT.

Improvement in Mitral Regurgitation Versus Long-Term Follow-Up

In the current study, eGFR, LVESV response, and MR improvement were all independently associated with improved long-term outcome (survival) after CRT. Previously, several studies have shown that a (significant) reduction in...
LVESV at 6 months follow-up resulted in superior long-term survival after CRT.33,34 Yu et al reported that patients with a reduction in LVESV ≥10% after CRT had significantly better survival compared to patients with LVESV reduction <10% whereas a more recent study by Ypenburg et al even related the extent of LV reverse remodeling to long-term prognosis after CRT. These observations are confirmed by the current findings, where patients with a volumetric response after CRT (defined as a reduction ≥15% in LVESV at 6 months follow-up) had significantly better long-term prognosis. A novel finding in the current study is that in addition to this significant LV reverse remodeling, a reduction of ≥1 grade of MR 6 months after CRT (MR improvement) also resulted in superior survival during long-term follow-up (log rank P<0.001). Specifically, the 1- and 2-year survival rates were 97% and 92% in MR improvers compared with 88% and 67% in MR nonimprovers. More importantly, this beneficial survival effect of MR improvement was independent of other characteristics, including LVESV response at 6 months follow-up. This is the first study to establish a relation between improvement in MR at 6 months follow-up and superior survival during long-term follow-up after CRT. Possible explanations for this improved survival can be the further decrease in afterload induced by the reduction in MR or the interplay between reduction in MR and LV reverse remodeling. However, the survival benefit of MR improvement was independent of LVESV response at 6 months follow-up.

Conclusions

The observations in the present study indicate that CRT reduces the severity of MR at 6-month follow-up in heart failure patients with moderate-severe functional MR who are at high risk for mitral valve surgery. Applying CRT in this specific group may yield a new therapeutic option for MR. More importantly, patients with a reduction ≥1 grade of MR (MR improvers) had superior survival during long-term follow-up. This implicates a sustained survival benefit of CRT for heart failure patients with moderate-severe functional MR.

Disclosures

Professor Bax received grants from Medtronic, Biotronik, Boston Scientific, BMS Medical Imaging, St. Jude Medical, Edwards Life Sciences, and GE Healthcare. Professor Schalij received grants from Biotronik, Medtronic, and Boston Scientific. Dr Delgado receives consultancy fees from St. Jude Medical. The other authors report no conflicts.

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**CLINICAL PERSPECTIVE**

In heart failure patients with ischemic or nonischemic cardiomyopathy, functional mitral regurgitation (MR) is a frequent finding that has important prognostic implications. Functional MR can be treated surgically by means of restrictive annuloplasty with or without additional surgical left ventricular remodeling. However, the beneficial effect of this procedure on long-term mortality has not been clearly demonstrated, and many of these patients may not be referred for or are denied mitral valve surgery because of the high operative mortality risk. The current study sought to investigate the effect of cardiac resynchronization therapy (CRT) on moderate-severe functional MR and whether the reduction in severity of MR after CRT positively influenced long-term prognosis (survival). In 85 heart failure patients with moderate-severe functional MR, a significant reduction in extent of MR was observed after CRT, and particularly 42 patients (49%) improved ≥1 grade of MR. Importantly, improvement in MR was a strong independent prognostic factor of improved survival (hazard ratio, 0.35, P=0.043). These findings demonstrate that CRT may improve MR in heart failure patients with moderate-severe functional MR and high risk for surgery. Secondly, the current study showed for the first time that the improvement in MR results in superior survival during long-term follow-up independently of other known prognostic factors. Therefore, CRT may yield a valuable therapeutic option for heart failure patients with moderate-severe functional MR but with a high operative risk.
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Verschiedene Autoren haben in Versuchsreihen gezeigt, dass die Verabreichung von Acetylcystein zu einer Risikoreduktion bei Contrast-Induced Nephropathy (CIN) führen kann. Allerdings haben die Ergebnisse der klinischen Studien dazu geführt, dass Acetylcystein nicht routinemäßig empfohlen werden sollte.


심부전증에 중등도 이상의 기능성 MR이 동반된 경우, 우선 약물 치료로 MR의 호전을 기대하지만 많은 환자에서 MR이 지속되고 호흡곤란 등의 증상을 호소한다. 이러한 환자들에게서 숭모판륜 성형술 등의 수술적 치료를 고려할 수 있지만, 너무 높은 수술 위험 때문에 실제 수술이 이루어지거나 환자가 수술에 동의하는 경우는 적다. 또한 기능성 MR에서 숭모판 수술이 예후를 개선할 수 있는지도 명확하지 않아 치료지침에서도 분명한 적응증을 제시하지 못하고 있다.


CRT의 가장 큰 제한점으로는 CRT의 적응증이 되는 심부전 환자 중에서 nonresponder의 비율이 30%를 넘는다는 점이다. 이러한 nonresponse는 부적절한 좌심실 lead의 위치 및 scar tissue가 얼마나 넓게 분포하는지 등에 영향을 받는 것으로 알려져 있고, 이러한 인자들이 CRT 후 MR의 변화에도 관여할 것으로 예상되지만, 아직까지 CRT 후 MR의 변화를 예측할 수 있는 지표는 알려진 바 없다. 또한 본 연구의 MR 호전군에서 MR 비호전군에 비해 비허혈성 심부전의 빈도가 유의하게 높았는데, 이러한 심부전 원인의 차이가 CRT에 대한 반응 및 MR 변화에 영향을 주는 가능성이 있다. 본 연구의 제한점으로는 CRT 사전에 약물 치료를 시행한 기간에 대한 정보가 전혀 없어서 각각의 심부전 환자간에 비교하기 어렵다. 또한 본 연구는 CRT의 MR 감소 효과 및 장기 예후에 대한 효과가 단기에서만 나타날 수 있다는 점이다. 본 연구 결과에 비추어 CRT의 적응증이 되면서 약물 치료에 반응하지 않는 기능성 MR이 동반된 심부전 환자들에서 CRT는 우선적으로 고려될 수 있는 치료법이다.
Cardiac Resynchronization Therapy as a Therapeutic Option in Patients With Moderate-Severe Functional Mitral Regurgitation and High Operative Risk

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**Background**—Functional mitral regurgitation (MR) is a common finding in heart failure patients with dilated cardiomyopathy and has important prognostic implications. However, the increased operative risk of these patients may result in low referral or high denial rate for mitral valve surgery. Cardiac resynchronization therapy (CRT) has been shown to have a favorable effect on MR. Aims of this study were to (1) evaluate CRT as a therapeutic option in heart failure patients with functional MR and high operative risk and (2) investigate the effect of MR improvement after CRT on prognosis.

**Methods and Results**—A total of 98 consecutive patients with moderate-severe functional MR and high operative risk underwent CRT according to current guidelines. Echocardiography was performed at baseline and 6-month follow-up; severity of MR was graded according to a multiparametric approach. Significant improvement of MR was defined as a reduction ≥1 grade. All-cause mortality was assessed during follow-up (median 32 [range 6.0 to 116] months). Thirteen patients (13%) died before 6-months follow-up. In the remaining 85 patients, significant reduction in MR was observed in all evaluated parameters. In particular, 42 patients (49%) improved ≥1 grade of MR and were considered MR improvers. Survival was superior in MR improvers compared to MR nonimprovers (log rank \( P < 0.001 \)). Mitral regurgitation improvement was an independent prognostic factor for survival (hazard ratio 0.35, confidence interval 0.13 to 0.94; \( P = 0.043 \)).

**Conclusions**—Cardiac resynchronization therapy is a potential therapeutic option in heart failure patients with moderate-severe functional MR and high risk for surgery. Improvement in MR results in superior survival after CRT. (Circulation. 2011;124:912-919.)

Key Words: biventricular pacing ▪ cardiac resynchronization therapy ▪ mitral regurgitation ▪ prognosis

Functional mitral regurgitation (MR) is a common finding in heart failure patients with ischemic or nonischemic dilated cardiomyopathy.\(^1\)\(^-\)\(^2\) More importantly, the presence of MR has important prognostic implications in these patients.\(^1\)\(^\)\(^-\)\(^3\) The initial strategy of treating MR is optimization of medical therapy (afterload reduction and treatment of fluid load). However, in many patients significant functional MR persists and surgery may be the final option to reduce the extent of MR. The main surgical technique for treatment of functional MR is restrictive annuloplasty, with or without additional surgical left ventricular (LV) remodeling. In many of the patients, however, the increased operative mortality risk may result in either a low referral or high denial rate for mitral valve surgery. A recent study by Bach et al reported a nonreferral or denial rate for surgery as high as 84% in patients with moderate-to-severe or severe functional MR.\(^4\) Moreover, it is currently unclear whether mitral valve surgery improves prognosis in this specific group of patients.\(^5\) As a result, indications for mitral valve surgery in heart failure patients with functional MR are not well defined by any currently available guideline.\(^6\)

**Clinical Perspective on p 114**

Conversely, cardiac resynchronization therapy (CRT) has been shown to have a favorable effect on functional MR. There are several studies that have demonstrated a reduction in extent of functional MR after CRT.\(^7\)\(^-\)\(^12\) Most of these studies, however, were performed in patients with only mild-moderate MR, and therefore less is known about the effects of CRT in patients with moderate-severe functional MR. Furthermore, these studies were limited to changes at midterm (6 months) follow-up, and therefore no data exist...
with regard to the potential beneficial effects of reduction in M R on long-term prognosis. Consequently, the aims of this study were (1) to evaluate the role of CRT as an alternative therapeutic option in heart failure patients with moderate-severe functional M R and high operative risk and (2) to investigate the effect of reduction in severity of M R after CRT on long-term prognosis.

**Methods**

**Patient Population and Data Collection**
A total of 98 consecutive patients with moderate-severe functional M R and high operative risk were included. These patients are part of an ongoing registry and were referred for CRT according to the current guidelines. Patient data were prospectively collected in the departmental Cardiology Information System (EPD-Vision, Leiden University Medical Center, Leiden, the Netherlands).

Cause of heart failure was considered ischemic in the presence of significant coronary artery disease (≥50% stenosis in ≥1 of the major coronary arteries) and/or a history of myocardial infarction or prior revascularization. The protocol was as follows: In all patients, clinical status was assessed before implantation and at 6 months follow-up. Extensive echocardiography was performed at baseline and repeated 6 months after CRT to (1) quantify LV volumes and function and (2) evaluate the severity of M R. After the 6-month follow-up, patients were scheduled for regular visits to the outpatient clinic.

**Clinical Evaluation**
In all patients, evaluation of heart failure symptoms according to the New York Heart Association (NYHA) classification was performed. Assessment of quality of life was performed using the Minnesota Living with Heart Failure Questionnaire (high scores indicating poor quality of life), and when possible exercise capacity was measured using the 6-minute walk test. In addition, operative risk was assessed by means of the logistic Euroscore. Estimated glomerular filtration rate (eGFR) was calculated using the standard formula by Cockcroft and Gault and expressed in mL \( \cdot \) min\(^{-1} \cdot \) 1.73 m\(^{-2}\). Finally, outcome data were collected by chart review, device interrogation, and telephone contact. Primary end point during long-term follow-up was death from any cause.

**Echocardiography**
All patients underwent echocardiography in the left lateral decubitus position before and 6 months after CRT implantation. Imaging was performed using a commercially available echocardiographic system (VIVID 7, General Electric Vingmed Ultrasound, Milwaukee, WI). Images were obtained using a 3.5 MHz transducer at a depth of 16 cm in the parasternal and apical (2-, 3-, and 4-chamber) views. All images were recorded digitally in cine-loop format and analyzed offline with commercial software (EchoPac 108.1.5, General Electric Vingmed Ultrasound).

**Left Ventricular Volumes and Function Analysis**
LV end-diastolic and LV end-systolic volumes (LVEDV and LVE ESV, respectively) were determined from the conventional apical 2- and 4-chamber views, and LV ejection fraction (LVEF) was calculated using the biplane Simpson technique. Volumetric response to CRT was defined as a reduction ≥15% in LVE ESV at 6 months follow-up.

**Assessment of Mitral Regurgitation Severity**
Following current guidelines, we assessed the severity of M R using a multiparametric approach, which combined the following measurements: (1) vena contracta width (VCW), measured as the narrowest portion of the M R color Doppler jet in a zoomed, optimized parasternal long-axis view or in the apical 4-chamber view; (2) the ratio of the jet area to the left atrium (LA) area measured by planimetry in the 4-chamber view; (3) the effective regurgitant orifice area (EROA) calculated with the proximal isovelocity surface area method. The color Doppler images were acquired using a Nyquist limit of 30 to 60 cm/s and a color gain that just eliminates random color speckle from nonmoving regions. Severity of M R was defined using a multiparametric approach according to current guidelines and graded on a 4-point scale: mild=1+, moderate=2+, moderate-severe=3+, and severe=4+. Improvement in M R was defined as a reduction ≥1 grade 6 months after CRT. In addition, as a measure of mitral valve deformation, valvar tenting area was measured from the parasternal long-axis view at midsystole as the area enclosed between the annular plane and mitral leaflets. Left atrium volumes were measured form the 2- and 4-chamber views using the biplane Simpson technique. Finally, estimated systolic pulmonary artery pressure (SPAP) was derived from the right ventricular to right atrial pressure gradient or tricuspid regurgitant jet gradient and calculated with the modified Bernoulli equation.

**Table 1. Patient Characteristics (n=98)**

<table>
<thead>
<tr>
<th>Age, y</th>
<th>71 ± 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n (%)</td>
<td>72 (74)</td>
</tr>
<tr>
<td>Cause of heart failure, n (%)</td>
<td>62 (63)</td>
</tr>
<tr>
<td>Ischemic</td>
<td>36 (37)</td>
</tr>
<tr>
<td>Nonischemic</td>
<td>26 ± 13</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>51 ± 22</td>
</tr>
<tr>
<td>eGFR, mL ( \cdot ) min(^{-1} \cdot ) 1.73 m(^{-2})</td>
<td>18 (18)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>206 ± 80</td>
</tr>
<tr>
<td>Logistic Euroscore, %</td>
<td>23 ± 7</td>
</tr>
<tr>
<td>NYHA class</td>
<td>19 (19)</td>
</tr>
<tr>
<td>6 MWT, m</td>
<td>111 ± 0.4</td>
</tr>
<tr>
<td>QoL score</td>
<td>49 (50)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>49 (50)</td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td>57 (58)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>86 (88)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>86 (88)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>93 (95)</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>93 (95)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>93 (95)</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean±SD. eGFR indicates estimated glomerular filtration rate; NYHA, New York Heart Association; 6 MWT, 6-minute walk test; QoL, quality of life; LVEDV, left ventricular end-diastolic volume; LVE ESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; and ACE, angiotensin-converting enzyme.

**Statistical Analysis**
Continuous data are presented as mean±SD, and dichotomous data are presented as n (%). Comparison of data at baseline and 6-month follow-up was performed with the paired-samples t test. Comparison of data between patient groups was performed using the independent-samples t test for continuous data. The Fisher exact tests or χ² tests were used as appropriate to compare dichotomous data. Analysis of variance for repeated measurements, including interaction between group and time, was applied for comparison of data between patient groups at baseline and 6 months follow-up. The event-free survival of patients was evaluated with the Kaplan-Meier
method and the log rank test. The effect of improvement in MR on event-free survival, adjusted for other variables, was investigated using the Cox proportional hazards model. Variables that showed a statistically significant effect in the univariate analyses were entered in the multivariate Cox proportional hazards model. The proportional hazards assumption was checked for continuous variables by visual inspection of scaled Schoenfeld residuals and for categorical variables by visual inspection of log-log plots. All analyses were performed with SPSS for Windows, version 16.0 (SPSS, Chicago, IL). All statistical tests were 2-sided. A \( P \) value \( < 0.05 \) was considered statistically significant.

Results

Patient Characteristics

Baseline characteristics of the patient population are presented in Table 1. The majority of patients were men (74%), and the underlying cause of heart failure was ischemic cardiomyopathy in 62 patients (63%). All patients had moderate-severe MR (63% grade 3+ and 37% grade 4+) with a central jet secondary to significant LV dilatation and dysfunction. Furthermore, all patients were characterized by a high operative risk (logistic Euroscore 26+13%, mean eGFR 51+22 mL·min\(^{-1}\)·1.73 m\(^{-2}\), diabetes mellitus in 19% of cases). Optimal medical therapy was administered to all patients, if tolerated. Implantation of a CRT device was successful in all patients, and no procedure-related complications were observed. All devices were programmed to simultaneous biventricular pacing during the first 6 months of follow-up. Before the 6-month follow-up, 13 patients died (10 patients died because of heart failure, 2 patients died because of severe infection, and 1 patient died because of a malignancy). Therefore, further analysis (baseline versus follow-up) was performed in the remaining 85 patients. Of note, patients who died before the 6-month follow-up had a higher logistic Euroscore (34+15 versus 24+12), lower eGFR (40+15 mL·min\(^{-1}\)·1.73 m\(^{-2}\) versus 53+23 mL·min\(^{-1}\)·1.73 m\(^{-2}\)) and were in a higher NYHA class (3.4+0.5 versus 3.1+0.3) at baseline compared with patients who survived the first 6 months of follow-up.

Clinical and Left Ventricular Functional Changes After 6 Months of Cardiac Resynchronization Therapy

At 6-month follow-up, the mean NYHA class improved from 3.1+0.3 to 2.1+0.7 (\( P < 0.001 \)). In addition, the quality of life score decreased from 38+18 to 24+17 (\( P < 0.001 \)) whereas distance covered in the 6-minute walk test increased from 283+109 m to 368+120 m (\( P < 0.001 \)). Significant LV reverse remodeling was observed at 6-month follow-up, as shown by a decrease in LVEDV from 261+88 mL at baseline to 233+81 mL at follow-up and a decrease in LVESV from 205+81 mL to 166+72 mL (both \( P < 0.001 \)). Furthermore, an increase in LVEF from 23+7% at baseline to 30+9% at follow-up was noted (\( P < 0.001 \)). Volumetric response to CRT (reduction \( \approx 15\% \) in LVESV at 6-month follow-up) was observed in 54 patients (55%).

Changes in Mitral Regurgitation Severity After 6 Months of Cardiac Resynchronization Therapy

Severity of MR improved significantly according to all evaluated parameters (Figure 1). The VCW decreased from

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Figure 1. Changes in severity of MR at 6-month follow-up. Improvement in severity of MR at 6 months follow-up was observed in all evaluated parameters (A, VCW; B, EROA; C, tenting area; D, LA volume; E, Jet area/LA volume; F, SPAP). Error bars represent standard deviation. VCW indicates vena contracta width; EROA, effective regurgitant orifice area; LA, left atrium; and SPAP, systolic pulmonary artery pressure.
0.74 ± 0.15 cm at baseline to 0.59 ± 0.21 cm at follow-up (P < 0.001) whereas the EROA decreased from 0.51 ± 0.16 cm² to 0.43 ± 0.18 cm² (P = 0.001). Tenting area decreased from 7.2 ± 2.0 cm² at baseline to 6.2 ± 2.0 cm² at follow-up (P < 0.001), and the LA volume decreased from 103 ± 38 mL to 91 ± 32 mL (P < 0.001). Finally, the regurgitant jet area ratio decreased from 51 ± 14% at baseline to 41 ± 18% at follow-up (P < 0.001) and mean SPAP decreased from 35 ± 10 mm Hg to 31 ± 10 mm Hg (P < 0.001). An example of significant improvement in severity of MR is displayed in Figure 2.

Figure 2. Example of a patient with a significant improvement in MR at 6-month follow-up. At baseline, the MR jet area exceeded 80% of the LA area, and the EROA was 0.61 cm². A, Four-chamber view; B, parasternal long-axis view. At 6-month follow-up, the jet area decreased to 10% of the LA area and the EROA was 0.19 cm². C, Four-chamber view; D, para-sternal long-axis view.

Mitr al Regurgitation Improvers Versus Mitr al Regurgitation Nonimprovers After Cardiac Resynchronization Therapy

At 6-month follow-up, MR improvement (reduction ≥ 1 grade of MR as previously described) was noted in 42 patients (49%). These patients were therefore considered MR improvers. Baseline clinical characteristics were comparable between MR improvers and MR nonimprovers. However, ischemic cause of heart failure was more frequently observed among MR nonimprovers (Table 2). In addition, MR improvers had slightly less symptomatic heart failure (according to the NYHA functional class).

Comparison of clinical and echocardiographic data between MR improvers and nonimprovers, both at baseline and 6-month follow-up, is displayed in Table 3. At 6-month follow-up, both MR improvers and MR nonimprovers had an improvement in clinical characteristics. However, these improvements were more pronounced in MR improvers. All baseline echocardiographic parameters were comparable between MR improvers and nonimprovers. At 6-month follow-up, reductions in LV volumes and an increase in LVEF were observed in both groups. Of note, 39 MR improvers (93%) also had significant LV volumetric response, versus only 15 patients (35%) in the MR nonimprovers group (P < 0.001). By definition, MR improvers had a significant decrease in MR severity at 6-month follow-up.

Table 2. Clinical Characteristics of MR Improvers and Nonimprovers

<table>
<thead>
<tr>
<th>Variable</th>
<th>MR Improvers (n=42)</th>
<th>MR Nonimprovers (n=43)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70 ± 8</td>
<td>70 ± 7</td>
<td>0.914</td>
</tr>
<tr>
<td>Men/Women, n/n</td>
<td>28/14</td>
<td>34/9</td>
<td>0.229</td>
</tr>
<tr>
<td>Cause of heart failure, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>20 (48)</td>
<td>32 (74)</td>
<td>0.015</td>
</tr>
<tr>
<td>Nonischemic</td>
<td>22 (52)</td>
<td>11 (26)</td>
<td></td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>165 ± 33</td>
<td>165 ± 28</td>
<td>0.942</td>
</tr>
<tr>
<td>eGFR, mL · min⁻¹ · 1.73 m⁻²</td>
<td>55 ± 23</td>
<td>51 ± 23</td>
<td>0.432</td>
</tr>
<tr>
<td>Diabetes mellitus, n</td>
<td>5 (12)</td>
<td>10 (23)</td>
<td>0.255</td>
</tr>
<tr>
<td>Medication, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>40 (95)</td>
<td>41 (95)</td>
<td>0.981</td>
</tr>
<tr>
<td>Diuretics</td>
<td>38 (90)</td>
<td>39 (91)</td>
<td>0.972</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>35 (83)</td>
<td>38 (88)</td>
<td>0.505</td>
</tr>
<tr>
<td>β-blockers</td>
<td>25 (60)</td>
<td>25 (58)</td>
<td>0.897</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>20 (48)</td>
<td>24 (56)</td>
<td>0.450</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean ± SD.
MR indicates mitral regurgitation; eGFR, estimated glomerular filtration rate; and ACE, angiotensin-converting enzyme.
grade from 3.3±0.5 to 1.8±0.6, and this was evidenced by significant improvement in all evaluated parameters. Conversely, MR nonimprovers showed (by definition) no improvement in MR grade from 3.3±0.5 to 3.4±0.6.

### Improvement in Mitral Regurgitation and Long-Term Prognosis After Cardiac Resynchronization Therapy

To evaluate whether improvement in MR has prognostic importance after CRT, MR improvement was investigated in relation to all-cause mortality during long-term follow-up (median 32 [range 6.0 to 116] months). During this follow-up period, 34 patients (40%) died. Survival was superior in MR improvers compared with MR nonimprovers (log rank P<0.001; Figure 3).

Respective 1- and 2-year survival rates were 97% and 92% in MR improvers compared with 88% and 67% in MR nonimprovers (log rank P=0.117 for comparison at 1-year follow-up and log rank P=0.013 at 2-year follow-up). Additionally, MR improvement was tested as an independent predictor for all-cause mortality using a multivariate Cox proportional hazards model. In univariate analysis, MR improvement reached a crude hazard ratio (HR) of 0.21 (95% confidence interval 0.09 to 0.49, P=0.019). After correction for other significant variables in the univariate analysis, MR improvement remained a strong independent predictor of survival after CRT, with a corrected HR of 0.35 (95% confidence interval 0.13 to 0.94, P=0.043, Table 4).

### Discussion

The findings of the present study can be summarized as follows: (1) CRT reduces severity of MR at 6-month follow-up in heart failure patients with moderate-severe functional MR and at high risk for mitral valve surgery, and (2) improvement in MR results in superior survival during long-term follow-up.

### Functional Mitral Regurgitation in Heart Failure

In heart failure patients with impaired LV systolic function, MR is a frequent finding. It is estimated that nearly half of these patients have some degree of MR, and in about 30% of these cases, extent of MR can be graded as moderate or severe.1,2,23 In most patients, a structurally normal mitral valve is often unable to maintain a normal coaptation between the leaflets. The left ventricle is dilated and the diastolic function and regional wall motion abnormalities are impaired, resulting in a functional MR. Mitral valve regurgitation is a marker of LV dysfunction and is associated with increased morbidity and mortality.1,2,24 It is estimated that nearly half of all heart failure patients have some degree of MR and in about 30% of these cases, extent of MR can be graded as moderate or severe.1,2,23

While the correlation of functional MR with adverse outcomes is well established, there are limitations of this approach. First, the degree of MR is not necessarily a good indicator of the true extent of LV dysfunction because the severity of regurgitation may be overestimated in the setting of decreased LV compliance and increased afterload.23 Second, the degree of MR may not reflect the true extent of LV dysfunction, as LV dysfunction may be present but not associated with an increase in regurgitation.23 Third, the degree of MR may not reflect the true extent of LV dysfunction, as LV dysfunction may be present but not associated with an increase in regurgitation.

### Figure 3

Kaplan–Meier survival curves for time to all-cause mortality in MR improvers versus MR nonimprovers. During long-term follow-up, survival was superior in MR improvers compared with MR nonimprovers; log rank P<0.001. Respective 1- and 2-year survival rates were 97% and 92% in MR improvers compared with 88% and 67% in MR nonimprovers. MR indicates mitral regurgitation.
valve is present, but the regurgitation is secondary to changes in LV geometry caused by LV remodeling (dilatation). This specific type of MR is referred to as functional MR.6,23 There have been several studies that have evaluated the effect of mitral valve surgery in patients with heart failure and functional MR.24–26 Wu et al studied 682 patients with significant MR and LV systolic dysfunction.24 Out of these 682 patients, 419 were considered candidates for surgical correction. Surprisingly, only 126 of these patients (30%) eventually underwent mitral valve repair. Mentioned reasons for nonreferral or denial for surgery included cardiogenic shock, renal failure, significant valvular lesion other than MR, and the fact that patients were felt to be too weak to undergo surgery after evaluation by cardiac surgeon or cardiologist. Other reasons included the coexistence of conditions that increased the risk of cardiac surgery. During long-term follow-up, 112 patients (38%) who were not referred to or were denied for surgery died versus 61 of those who had undergone mitral valve surgery (48%; P=NS). It was therefore concluded that there was no significant survival benefit in the surgical group. The finding that 70% of patients were either not referred or denied for mitral valve surgery was confirmed by another recent study from the same group.4

Effects of Cardiac Resynchronization Therapy on Functional Mitral Regurgitation

Contrasting with the above-mentioned results on surgery for functional MR, previous studies on the effects of CRT have not only demonstrated improved survival27 but also a significant reduction in extent of functional MR after CRT.7–12 Most of the studies on changes in MR after CRT were single-center studies with limited numbers of patients. Nevertheless, results among these studies are consistent, and several explanations for improvement in MR, including the immediate effect of resynchronization and improvement of LV contraction (inducing synchronized mechanical activation of papillary muscle insertion sites),8,10 and the more delayed effect of favorable changes in mitral valve geometry (LV reverse remodeling)10,11 have been proposed. Moreover, in the Cardiac Resynchronisation in Heart Failure (CARE-HF) trial, which randomized 813 patients to receive either biventricular pacing in addition to optimized medical therapy or optimized medical therapy alone, there was a significantly greater reduction in MR (measured by the regurgitant jet area ratio) in patients who received CRT compared with patients on optimized medical therapy alone 3 months after CRT (difference in means 5.1%, P < 0.001).27 Finally, pooled data from several major studies including 357 patients implanted with a CRT device, with a follow-up of at least 6 months, showed a reduction in functional MR (measured by the regurgitant jet area) of 30% to 40% after CRT.28 The above-mentioned results clearly demonstrate the beneficial effects of CRT on functional MR.

Several contributing factors to nonresponse to CRT, such as inappropriate LV lead positioning and, in patients with ischemic cardiomyopathy, the extent and location of scar tissue, have been previously reported.29–32 These factors might also have a significant effect on the changes in MR after CRT. Positioning the LV pacing lead at the optimal site (latest activated myocardial segment) may improve MR during CRT by any of the 2 mechanisms described above (synchronized mechanical activation of papillary muscle insertion sites and LV reverse remodeling during follow-up). Conversely, the presence of significant scar tissue may limit the extent of LV reverse remodeling after CRT and therefore also prevent the improvement in MR. In addition, positioning the LV lead at the level of a nonviable myocardial segment may significantly hamper the beneficial effect of CRT on LV remodeling and MR. Specific studies are needed to further explore the relationship between these different factors and the improvement of MR after CRT.

Improvement in Mitral Regurgitation Versus Long-Term Follow-Up

In the current study, eGFR, LVESV response, and MR improvement were all independently associated with improved long-term outcome (survival) after CRT. Previously, several studies have shown that a (significant) reduction in

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<th>Table 4. Uni- and Multivariate Cox Proportional Hazards Models for Time to All-Cause Mortality</th>
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<td>Age, y</td>
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<td>Men</td>
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<td>Ischemic cause</td>
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<td>NYHA class IV vs III</td>
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<td>Diabetes mellitus</td>
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<td>QRS duration, ms</td>
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<td>eGFR, mL·min⁻¹·1.73 m⁻²</td>
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<td>MR Improvement</td>
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<td>LVESV Response</td>
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HR indicates hazard ratio; CI, confidence interval; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; MR, mitral regurgitation; and LVESV, left ventricular end-systolic volume.
LVESV at 6 months follow-up resulted in superior long-term survival after CRT.33–35 Yu et al reported that patients with a reduction in LVESV $\geq 10\%$ after CRT had significantly better survival compared to patients with LVESV reduction $<10\%$ whereas a more recent study by Y penburg et al even related the extent of LV reverse remodeling to long-term prognosis after CRT. These observations are confirmed by the current findings, where patients with a volumetric response after CRT (defined as a reduction $\geq 15\%$ in LVESV at 6 months follow-up) had significantly better long-term prognosis. A novel finding in the current study is that in addition to this significant LV reverse remodeling, a reduction of $\geq 1$ grade of MR 6 months after CRT (MR improvement) also resulted in superior survival during long-term follow-up (log rank P $< 0.001$). Specifically, the 1- and 2-year survival rates were 97% and 92% in MR improvers compared with 88% and 67% in MR nonimprovers. More importantly, this beneficial survival effect of MR improvement was independent of other characteristics, including LVESV response at 6 months follow-up. This is the first study to establish a relation between improvement in MR at 6 months follow-up and superior survival during long-term follow-up after CRT. Possible explanations for this improved survival can be the further decrease in afterload induced by the reduction in MR or the interplay between reduction in MR and LV reverse remodeling. However, the survival benefit of MR improvement was independent of LVESV response at 6 months follow-up.

Conclusions

The observations in the present study indicate that CRT reduces the severity of MR at 6-month follow-up in heart failure patients with moderate-severe functional MR who are at high risk for mitral valve surgery. Applying CRT in this specific group may yield a new therapeutic option for MR. More importantly, patients with a reduction $\geq 1$ grade of MR (MR improvers) had superior survival during long-term follow-up. This implicates a sustained survival benefit of CRT for heart failure patients with moderate-severe functional MR.

Disclosures

Professor Bax received grants from Medtronic, Biotronik, Boston Scientific, BMS Medical Imaging, St. Jude Medical, Edwards Life Sciences, and GE Healthcare. Professor Schalij received grants from Biotronik, Medtronic, and Boston Scientific. Dr Delgado receives consultancy fees from St. Jude Medical. The other authors report no conflicts.

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**CLINICAL PERSPECTIVE**

In heart failure patients with ischemic or nonischemic cardiomyopathy, functional mitral regurgitation (MR) is a frequent finding that has important prognostic implications. Functional MR can be treated surgically by means of restrictive annuloplasty with or without additional surgical left ventricular remodeling. However, the beneficial effect of this procedure on long-term mortality has not been clearly demonstrated, and many of these patients may not be referred for or are denied mitral valve surgery because of the high operative mortality risk. The current study sought to investigate the effect of cardiac resynchronization therapy (CRT) on moderate-severe functional MR and whether the reduction in severity of MR after CRT positively influenced long-term prognosis (survival). In 85 heart failure patients with moderate-severe functional MR, a significant reduction in extent of MR was observed after CRT, and particularly 42 patients (49%) improved ≥ 1 grade of MR. Importantly, improvement in MR was a strong independent prognostic factor of improved survival (hazard ratio, 0.35, P = 0.043). These findings demonstrate that CRT may improve MR in heart failure patients with moderate-severe functional MR and high risk for surgery. Secondly, the current study showed for the first time that the improvement in MR results in superior survival during long-term follow-up independently of other known prognostic factors. Therefore, CRT may yield a valuable therapeutic option for heart failure patients with moderate-severe functional MR but with a high operative risk.