Chapter 26

Cardiac resynchronization therapy as a therapeutic option in patients with moderate-severe functional mitral regurgitation and high operative risk

van Bommel RJ, Marsan NA, Delgado V, Borleffs CJ, van Rijnsoever EP, Schalij MJ, Bax JJ

Circulation 2011;124(8):912-9

ABSTRACT

Background: Functional mitral regurgitation (MR) is a common finding in heart failure (HF) 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) showed to have a favorable effect on MR. Aims of this study were to: 1) evaluate CRT as a therapeutic option in HF patients with functional MR and high operative risk; and 2) investigate the effect of MR improvement after CRT on prognosis.

Methods: 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 multi-parametric approach. Significant improvement of MR was defined as a reduction ≥1 grade. All cause-mortality was assessed during follow-up (median 32 [6.0-116] months).

Results: Thirteen (13%) patients died before 6 months follow-up. In the remaining 85 patients, significant reduction in MR was observed in all evaluated parameters. In particular, 42 (49%) patients improved ≥1 grade of MR and were considered MR improvers. Survival was superior in MR improvers as compared to MR non-improvers, log rank $p<0.001$. MR improvement was an independent prognostic factor for survival (HR 0.35, C.I. 0.13-0.94, $p = 0.043$).

Conclusions: CRT is a potential therapeutic option in HF patients with moderate-severe functional MR and high risk for surgery. Improvement in MR results in superior survival after CRT.

INTRODUCTION

Functional mitral regurgitation (MR) is a common finding in heart failure patients with ischemic or non-ischemic 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 non-referral 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]

Conversely, cardiac resynchronization therapy (CRT) showed to have a favorable effect on functional MR. There are several studies that 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 mid-term (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.[13] Patient data were prospectively collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, the Netherlands).

Etiology of heart failure was considered ischemic in the presence of significant coronary artery disease (≥50% stenosis in 1 or more 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 months 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)[14] and when possible, exercise capacity was measured using the 6-minute walk test.[15] In addition, operative risk was assessed by means of the logistic Euroscore.[16] Estimated glomerular filtration rate (eGFR) was calculated using the standard formula by Cockcroft and Gault and expressed in ml/min/1.73m^2.[17] 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, USA). 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, Milwaukee, USA).

LV volumes and function analysis

LV end-diastolic (LVEDV) and LV end-systolic (LVESV) volumes were determined from the conventional apical 2- and 4-chamber views and LV ejection fraction (LVEF) was calculated using the biplane Simpson's technique.[18] Volumetric response to CRT was defined as a reduction ≥15% in LVESV at 6 months follow-up.[19]

Assessment of MR severity

According to the current guidelines,[20, 21] the severity of MR was assessed using a multi-parametric 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 (PISA) method. The color Doppler images were acquired using a Nyquist limit of 30-60 cm/sec, and a color gain that just eliminates random color speckle from non-moving regions. Severity of MR was defined using a multi-parametric approach, according to current guidelines,[21] and graded on a four-point scale: mild = 1+, moderate = 2+, moderate-severe = 3+ and severe = 4+. Improvement in MR was defined as a reduction ≥1 grade, 6 months after CRT. In addition, as a measure of MV 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. LA volumes were measured form the 2- and 4-chamber views using the biplane Simpson's 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.[22]

Statistical analysis

Continuous data are presented as mean±SD, and dichotomous data are presented as numbers and percentages. Comparison of data at baseline and 6 months 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. Fisher's exact tests or χ^2 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 two-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 male (74%) and the underlying cause of heart failure was ischemic cardiomyopathy in 62 (63%) patients. 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/1.73m^2, diabetes in 19% of cases). Optimal medical therapy was administered in 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 months follow-up, 13 patients died (10 patients died due to heart failure, 2 patients died due to severe infection and 1 patient died because of a malignancy). Therefore, further analysis (baseline vs. follow-up) was performed in the remaining 85 patients. Of note, patients that died before the 6 months follow-up had a higher logistic Euroscore (34±15 vs. 24±12), lower eGFR (40±15 ml/min/1.73m^2 vs. 53±23 ml/min/1.73m^2) and were in higher NYHA class (3.4±0.5 vs. 3.1±0.3) at baseline as compared to patients that survived the first 6 months of follow-up.

Clinical and LV functional changes after 6 months CRT

At 6 months follow-up, mean NYHA class improved from 3.1±0.3 to 2.1±0.7 ($p<0.001$). In addition, quality of life score decreased from 38±18 to 24±17 ($p<0.001$), while 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 months follow-up, as evidenced 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 months follow-up) was observed in 54 (55%) patients.

Table 1. Patient characteristics (n = 98)

Age (years)	71 ± 7
Male gender (n)	72 (74%)
Etiology of heart failure	
Ischemic	62 (63%)
Non-ischemic	36 (37%)
QRS duration (ms)	166 ± 29
eGFR (ml/min/1.73m^2)	51 ± 22
Diabetes (n, %)	18 (18%)
Logistic Euroscore (%)	26 ± 13
NYHA class	3.2 ± 0.4
6 MWT (m)	270 ± 111
QoL score	38 ± 19
LVEDV (ml)	262 ± 88
LVESV (ml)	206 ± 80
LVEF (%)	23 ± 7
Medication (n)	
Anticoagulants	93 (95%)
Diuretics	86 (88%)
ACE-inhibitors	86 (88%)
B-blockers	57 (58%)
Spironolactone	49 (50%)

6 MWT = 6-minute walk test; ACE = angiotensin-converting enzyme; eGFR = estimated glomerular filtration rate; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association; QoL = quality of life

Changes in MR severity after 6 months CRT

Severity of MR improved significantly according to all evaluated parameters (Figure 1). The VCW decreased from 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 mmHg to 31±10 mmHg (p = 0.001). An example of significant improvement in severity of MR is displayed in Figure 2.

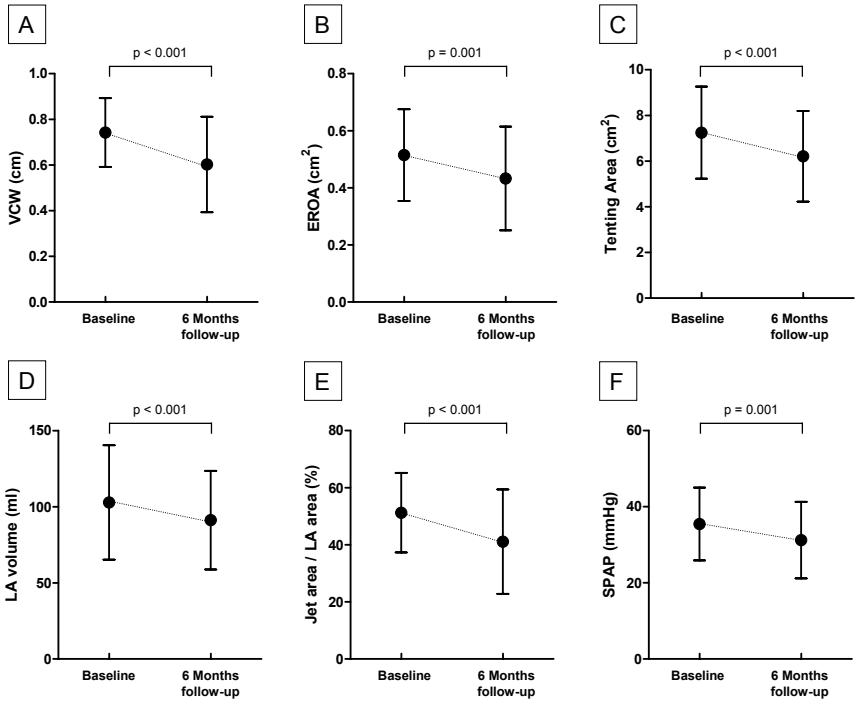


Figure 1. Changes in severity of MR at 6 months follow-up.

Improvement in severity of MR at 6 months follow-up was observed in all evaluated parameters. Error bars represent standard deviation. EROA = effective regurgitant orifice area; LA = left atrium; SPAP = systolic pulmonary artery pressure; VCW = vena contracta width.

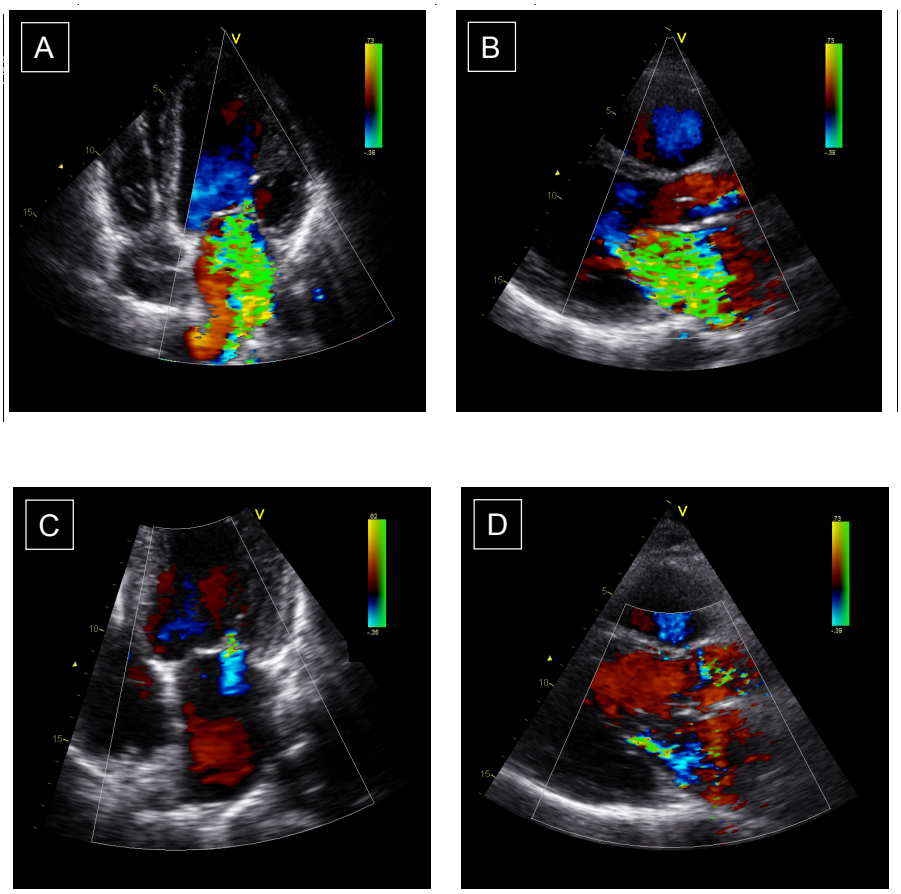


Figure 2. Example of a patient with a significant improvement in MR at 6 months follow-up.
At baseline, the MR jet area exceeded 80% of the left atrium area and the effective regurgitant orifice area (EROA) was 0.61 cm^2 (Panels A [4-chamber view] and B [parasternal long-axis view]). At 6 months follow-up, the jet area decreased to 10% of the left atrium area and the EROA was 0.19 cm^2 (Panels C [4-chamber view] and D [parasternal long-axis view]).

Table 2. Clinical characteristics of MR improvers and non-improvers

Variable	MR improvers (n = 42)	MR non-improvers (n = 43)	p-value
Age (years)	70 ± 8	70 ± 7	0.914
Men / Women	28 / 14	34 / 9	0.229
Etiology of heart failure			
Ischemic	20 (48%)	32 (74%)	**0.015**
Non-ischemic	22 (52%)	11 (26%)	
QRS duration (ms)	165 ± 33	165 ± 28	0.942
eGFR (ml/min/1.73m^2)	55 ± 23	51 ± 23	0.432
Diabetes (n)	5 (12%)	10 (23%)	0.255
Medication (n)			
Anticoagulants	40 (95%)	41 (95%)	0.981
Diuretics	38 (90%)	39 (91%)	0.972
ACE-inhibitors	35 (83%)	38 (88%)	0.505
B-blockers	25 (60%)	25 (58%)	0.897
Spironolactone	20 (48%)	24 (56%)	0.450

6 MWT = 6-minute walk test; ACE = angiotensin-converting enzyme; eGFR = estimated glomerular filtration rate; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association; QoL = quality of life

Table 3. Changes in clinical and echocardiographic characteristics of MR improvers and non-improvers at 6 months follow-up

Variable	MR improvers (n = 42)		MR non-improvers (n = 43)		p-value between groups	p-value interaction group and time
	Baseline	Follow-up	Baseline	Follow-up		
NYHA class	3.0 ± 0.2	1.9 ± 0.7‡	3.2 ± 0.4	2.3 ± 0.6‡	0.005	0.117
6 MWT (m)	299 ± 113	407 ± 121*	266 ± 105	329 ± 106‡	0.022	0.061
QoL score	35 ± 17	19 ± 16*	42 ± 18	28 ± 17*	0.019	0.783
LVEDV (ml)	255 ± 84	214 ± 78‡	267 ± 93	252 ± 81*	0.174	0.004
LVESV (ml)	201 ± 80	146 ± 69‡	208 ± 83	187 ± 70†	0.151	<0.001
LVEF (%)	23 ± 7	33 ± 10‡	23 ± 6	27 ± 7†	0.039	<0.001
VCW (cm)	0.73 ± 0.14	0.44 ± 0.16†	0.74 ± 0.17	0.73 ± 0.13	<0.001	<0.001
EROA (cm^2)	0.51 ± 0.16	0.31 ± 0.12*	0.52 ± 0.16	0.54 ± 0.16	0.002	<0.001
TA (cm^2)	7.1 ± 2.1	5.5 ± 1.7‡	7.4 ± 1.9	7.1 ± 2.0*	0.033	<0.001
LA volume (ml)	102 ± 43	78 ± 27‡	104 ± 32	104 ± 32	0.050	<0.001
Jet area / LA area (%)	51 ± 14	29 ± 15*	52 ± 14	53 ± 13	<0.001	<0.001
SPAP (mmHg)	34 ± 10	25 ± 6*	37 ± 9	38 ± 9	<0.001	<0.001
MR grade	3.3 ± 0.5	1.8 ± 0.6*	3.3 ± 0.5	3.4 ± 0.6	<0.001	<0.001

6 MWT = 6-minute walk test; EROA = effective regurgitant orifice area; LA = left atrium; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-diastolic volume; MR = mitral regurgitation; NYHA = New York Heart Association; QoL = quality of life; SPAP = systolic pulmonary artery pressure; TA = tenting area; VCW = vena contracta width

* $p<0.05$, baseline vs. follow-up, † $p = 0.001$, baseline vs. follow-up, ‡ $p<0.001$, baseline vs. follow-up

MR improvers vs. MR non-improvers after CRT

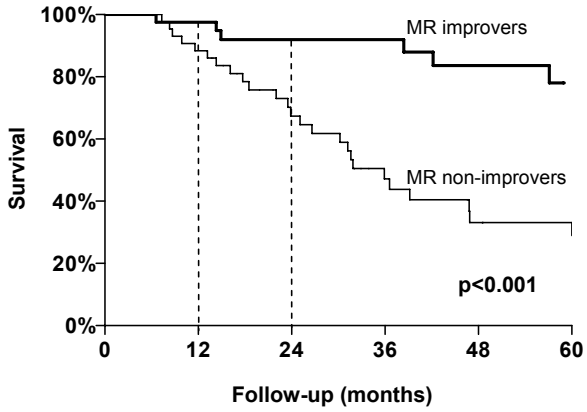
At 6 months follow-up, MR improvement (reduction ≥1 grade of MR as previously described) was noted in 42 (49%) patients. These patients were therefore considered MR improvers. Baseline clinical characteristics were comparable between MR improvers and MR non-improvers. However, ischemic etiology of heart failure was more frequently observed among MR non-improvers (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 non-improvers, both at baseline and 6 months follow-up, is displayed in Table 3. At 6 months follow-up, both MR improvers and MR non-improvers had an improvement in clinical characteristics. However, these improvements were more outspoken in MR improvers. All baseline echocardiographic parameters were comparable between MR improvers and non-improvers. At 6 months follow-up, reductions in LV volumes and an increase in LVEF were observed in both groups. Of note, 39 (93%) MR improvers also had significant LV volumetric response, vs. only 15 (35%) patients in the MR non-improvers group ($p<0.001$). By definition, MR improvers had a significant decrease in MR grade from 3.3±0.5 to 1.8±0.6, and this was evidenced by significant improvement in all evaluated parameters. Conversely, MR non-improvers showed (by definition) no improvement in MR grade from 3.3±0.5 to 3.4±0.6.

Improvement in MR and long-term prognosis after CRT

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 [6.0-116] months). During this follow-up period, 34 (40%) patients died. Survival was superior in MR improvers as compared to MR non-improvers, log rank $p<0.001$ (Figure 3).

Respective 1- and 2-year survival rates were 97% and 92% in MR improvers as compared with 88% and 67% in MR non-improvers (log rank $p = 0.117$ for comparison at 1 year follow-up and log rank $p = 0.013$ at 2 years 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 0.09-0.49, $p<0.001$). 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 0.13-0.94, $p = 0.043$, Table 4).



Patients at risk						
MR improvers	42	37	28	24	18	13
MR non-improvers	43	38	24	14	9	8

Figure 3. Kaplan-Meier survival curves for time to all-cause mortality in MR improvers versus MR non-improvers.
During long-term follow-up, survival was superior in MR improvers as compared to MR non-improvers, log rank p<0.001. Respective 1- and 2-year survival rates were 97% and 92% in MR improvers as compared with 88% and 67% in MR non-improvers.

Table 4. Uni- and multivariate Cox proportional hazards models for time to all-cause mortality

	Univariate		Multivariate	
	HR (95%-C.I.)	*p-value*	*HR (95%-C.I.)*	*p-value*
Age (years)	1.01 (0.97-1.05)	0.539		
Male gender	1.10 (0.57-2.12)	0.784		
Ischemic etiology	1.56 (0.85-2.89)	0.154		
NYHA class IV vs. III	2.42 (1.23-4.78)	**0.011**	1.01 (0.40-2.55)	0.981
Diabetes	1.63 (0.83-3.22)	0.156		
QRS duration (ms)	1.00 (0.99-1.01)	0.947		
eGFR (ml/min/1.73m^2)	0.98 (0.97-0.99)	**0.002**	0.98 (0.97-1.00)	**0.025**
MR improvement	0.21 (0.09-0.49)	**<0.001**	0.35 (0.13-0.94)	**0.043**
LVESV response	0.25 (0.12-0.50)	**<0.001**	0.42 (0.18-0.97)	**0.042**

C.I. = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; NYHA = New York Heart Association

DISCUSSION

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

Functional MR 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 around 30% of these cases, extent of MR can be graded as moderate or severe.[1, 3, 23] In most patients, a structurally normal mitral 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 which 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 non-referral or denial for surgery included cardiogenic shock, renal failure, significant valvular lesion other than MR and the fact that patients 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 or denied for surgery died, vs. 61 (48%) of those who had undergone MV surgery (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 CRT on functional MR

Contrasting the abovementioned results on surgery for functional MR, previous studies on the effects of CRT have not only demonstrated improved survival,[27] 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. Nonetheless, results among these studies are consistent and several explanations for improvement in MR, including the acute 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 MV geometry (LV reverse remodeling)[10, 11] have been proposed. Moreover, in the 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 that received CRT as compared to patients on optimized medical therapy alone, 3 moths 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 30–40% after CRT.[28] The abovementioned results clearly demonstrate the beneficial effects of CRT on (functional) MR.

Several contributing factors to non-response 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 non-viable 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 MR vs. 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 as compared to patients with LVESV reduction <10%, while 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 as compared with 88% and 67% in MR

non-improvers. 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 improves severity of MR at 6 months follow-up in heart failure patients with moderate-severe functional MR, who are at high risk for MV 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.

REFERENCES

1. Trichon BH, Felker GM, Shaw LK, Cabell CH, O'Connor CM. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. *Am J Cardiol* 2003;91:538-543.
2. Robbins JD, Maniar PB, Cotts W, Parker MA, Bonow RO, Gheorghiade M. Prevalence and severity of mitral regurgitation in chronic systolic heart failure. *Am J Cardiol* 2003;91:360-362.
3. Koelling TM, Aaronson KD, Cody RJ, Bach DS, Armstrong WF. Prognostic significance of mitral regurgitation and tricuspid regurgitation in patients with left ventricular systolic dysfunction. *Am Heart J* 2002;144:524-529.
4. Bach DS, Awais M, Gurm HS, Kohnstamm S. Failure of guideline adherence for intervention in patients with severe mitral regurgitation. *J Am Coll Cardiol* 2009;54:860-865.
5. Calafiore AM, Iaco AL, Tash A, Abukudair W, Di Mauro M. Mitral valve surgery for functional mitral regurgitation in patients with chronic heart failure--update of the results. *Thorac Cardiovasc Surg* 2010;58:131-135.
6. Vahanian A, Baumgartner H, Bax J et al. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J* 2007;28:230-268.
7. Breithardt OA, Sinha AM, Schwammenthal E et al. Acute effects of cardiac resynchronization therapy on functional mitral regurgitation in advanced systolic heart failure. *J Am Coll Cardiol* 2003;41:765-770.
8. Kanzaki H, Bazaz R, Schwartzman D, Dohi K, Sade LE, Gorcsan J, III. A mechanism for immediate reduction in mitral regurgitation after cardiac resynchronization therapy: insights from mechanical activation strain mapping. *J Am Coll Cardiol* 2004;44:1619-1625.
9. Lancellotti P, Melon P, Sakalihasan N et al. Effect of cardiac resynchronization therapy on functional mitral regurgitation in heart failure. *Am J Cardiol* 2004;94:1462-1465.
10. Ypenburg C, Lancellotti P, Tops LF et al. Mechanism of improvement in mitral regurgitation after cardiac resynchronization therapy. *Eur Heart J* 2008;29:757-765.
11. Solis J, McCarty D, Levine RA et al. Mechanism of decrease in mitral regurgitation after cardiac resynchronization therapy: optimization of the force-balance relationship. *Circ Cardiovasc Imaging* 2009;2:444-450.
12. Sitges M, Vidal B, Delgado V et al. Long-term effect of cardiac resynchronization therapy on functional mitral valve regurgitation. *Am J Cardiol* 2009;104:383-388.
13. Strickberger SA, Conti J, Daoud EG et al. Patient selection for cardiac resynchronization therapy: from the Council on Clinical Cardiology Subcommittee on Electrocardiography and Arrhythmias and the Quality of Care and Outcomes Research Interdisciplinary Working Group, in collaboration with the Heart Rhythm Society. *Circulation* 2005;111:2146-2150.
14. Rector TS, Kubo SH, Cohn JN. Validity of the Minnesota Living with Heart Failure questionnaire as a measure of therapeutic response to enalapril or placebo. *Am J Cardiol* 1993;71:1106-1107.
15. Guyatt GH, Sullivan MJ, Thompson PJ et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J* 1985;132:919-923.
16. Roques F, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. *Eur Heart J* 2003;24:881-882.
17. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16:31-41.
18. Schiller NB, Shah PM, Crawford M et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on

Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989;2:358-367.

19. Bleeker GB, Bax JJ, Fung JW et al. Clinical vs. echocardiographic parameters to assess response to cardiac resynchronization therapy. *Am J Cardiol* 2006;97:260-263.
20. Zoghbi WA, Enriquez-Sarano M, Foster E et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003;16:777-802.
21. Bonow RO, Carabello BA, Chatterjee K et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2008;52:e1-142.
22. Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. *Circulation* 1984;70:657-662.
23. Faber L, Lamp B. Mitral valve regurgitation and left ventricular systolic dysfunction: corrective surgery or cardiac resynchronization therapy? *Herzschrittmacherther Elektrophysiol* 2008;19 Suppl 1:52-59.
24. Wu AH, Aaronson KD, Bolling SF, Pagani FD, Welch K, Koelling TM. Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. *J Am Coll Cardiol* 2005;45:381-387.
25. Bach DS, Bolling SF. Early improvement in congestive heart failure after correction of secondary mitral regurgitation in end-stage cardiomyopathy. *Am Heart J* 1995;129:1165-1170.
26. Bolling SF, Pagani FD, Deeb GM, Bach DS. Intermediate-term outcome of mitral reconstruction in cardiomyopathy. *J Thorac Cardiovasc Surg* 1998;115:381-386.
27. Cleland JG, Daubert JC, Erdmann E et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539-1549.
28. Vinereanu D. Mitral regurgitation and cardiac resynchronization therapy. *Echocardiography* 2008; 25:1155-1166.
29. Ypenburg C, van Bommel RJ, Delgado V et al. Optimal left ventricular lead position predicts reverse remodeling and survival after cardiac resynchronization therapy. *J Am Coll Cardiol* 2008; 52:1402-1409.
30. Ypenburg C, Schalij MJ, Bleeker GB et al. Impact of viability and scar tissue on response to cardiac resynchronization therapy in ischaemic heart failure patients. *Eur Heart J* 2007;28:33-41.
31. Hummel JP, Lindner JR, Belcik JT et al. Extent of myocardial viability predicts response to biventricular pacing in ischemic cardiomyopathy. *Heart Rhythm* 2005;2:1211-1217.
32. van Bommel RJ, Schalij MJ, Bax JJ. Should the left ventricular pacing lead be positioned at the site of latest mechanical activation in cardiac resynchronization therapy? *J Cardiovasc Electrophysiol* 2009;20:536-538.
33. Ypenburg C, van Bommel RJ, Borleffs CJ et al. Long-term prognosis after cardiac resynchronization therapy is related to the extent of left ventricular reverse remodeling at midterm follow-up. *J Am Coll Cardiol* 2009;53:483-490.
34. Yu CM, Bleeker GB, Fung JW et al. Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after cardiac resynchronization therapy. *Circulation* 2005;112: 1580-1586.