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Over-time mitral regurgitation changes following cardiac resynchronization therapy

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ABSTRACT

Purpose: Mitral regurgitation (MR) is a leading cause of mortality in patients with heart failure (HF). Cardiac resynchronization therapy (CRT) has been shown to improve MR in these patients, but maintenance of MR improvement after CRT implantation has not yet been evaluated. We aimed to evaluate the post-CRT improvement pattern of MR in a 6-month follow-up period.
Materials and Methods: 65 consecutive patients scheduled for CRT implantation with inclusion criteria of moderate to severe heart failure, left ventricular ejection fraction (LVEF) ≤35%, and QRS duration >120 ms with left bundle branch block configuration were invited to participate. 60 patients with MR were registered. Clinical, electrocardiographic and echocardiographic evaluations were recorded before CRT implantation and 3 and 6 months after.
Results: We found significant improvement in MR score, NYHA class, QRS duration, LVEF and left ventricular end diastolic diameter (LVEDD) at the 3-month follow-up ($p<0.001$). These parameters also improved significantly ($p<0.0001$) between the 3 and 6-month follow-ups except for the MR score, which did not show any significant improvement.
Conclusion: MR improvement was sustained after CRT implantation between the 3 and 6-month follow-ups.

Key words: cardiac resynchronization therapy, congestive heart failure, mitral regurgitation.

INTRODUCTION

Cardiac resynchronization therapy (CRT) has been shown to improve hemodynamic parameters, exercise capacity, symptoms and quality of life, and also to reduce hospitalization among patients with heart failure (HF) who have prolongation of the QRS duration [1,2].

Functional mitral regurgitation (MR) is common in patients with chronic HF and represents a significant complication of end-stage cardiomyopathy. Correction of MR is a major issue in the management of patients with HF and has important prognostic implications, since the presence of moderate to severe mitral regurgitation is associated with a higher mortality rate among both the middle-aged and the elderly suffering from HF [3-9]. Ventricular asynchrony has been shown to be a factor influencing the severity of MR in patients with HF [10], and several studies have shown that CRT improves functional MR both acutely and in trials lasting up to 6 months [1,11-14], but a review of the literature indicates that little is known about the improvement pattern of MR by post-CRT duration. This motivated us to design a longitudinal study to assess MR changes over a period of 6 months in patients with moderate to severe HF.

MATERIALS AND METHODS

Study population and data collection:

We studied 65 consecutive patients with moderate to severe heart failure (New York Heart Association [NYHA] class III or IV), LV ejection fraction (LVEF) ≤35%, and QRS duration >120 ms with left bundle branch block configuration scheduled for the implantation of CRT devices in Jamaran Heart Hospital from 2004 to 2007. 60 patients who had MR

Table 1. **Basal Characteristics and the Comparison of Basal, 3-month and 6-month Characteristics.**

Parameters	Basal	3-mo follow-up	p value	6-mo follow-up	p value
Number (male/female)	60 (46/14)	60 (46/14)		60 (46/14)	
Age (yrs)*	59.5(1.3)				
Etiology (IC/NIC)	28/32				
Responder/Nonresponder		47/13		55/5	
NYHA class (I/II/III/IV)	0/0/57/8	2/44/17/2		16/46/3/0	
NYHA score*	3.1(0.05)	2.3(0.07)†	<0.001	1.8(0.07)†	<0.001
MR severity (No/I/II/III/IV)	0/24/24/10/2	23/28/7/2/0		27/28/5/0/0	
MR score*	1.83(0.11)	0.80(0.11)‡	<0.001	0.70(0.09)‡	<0.001
QRS duration (ms)*	144(2)	97(3)†	<0.001	83(1)†	<0.001
LVEF (%)*	21(1)	28(1)†	<0.001	37(1)†	<0.001
LVEDD (mm)*	6.8(0.08)	6.5(0.07)†	<0.001	5.9(0.07)†	<0.001

* Data are presented as mean (±SE).
† Significant between 3 and 6-month values.
‡ Nonsignificant between 3 and 6 month values.
IC; ischemic cardiomyopathy, NIC; non-ischemic cardiomyopathy, NYHA; New York Heart Association. LVEF; left ventricular ejection fraction, LVEDD; left ventricular end-diastolic diameter. mo; month, yrs; years, mm; millimeter, ms; millisecond.

were registered. The patients had a mean age of 59.5 ± 1.3 years (range 49 to 75; male/female ratio, 46/14). The etiology was considered to be ischemic cardiomyopathy (IC) in the presence of significant coronary artery disease (≥50% stenosis in one of the major epicardial coronary arteries) on coronary angiography, whereas patients with normal coronary arteries were classified as having non-ischemic cardiomyopathy (NIC). Improvement of ≥1 NYHA functional class after 3 or 6 months of follow-up was considered a response to CRT [15]. This study was approved by Jamaran Hospital Ethical Board and written consent was obtained from all patients.

All patients were evaluated clinically with a single cardiologist before CRT implantation and 3 and 6 months after. Standard 12-lead electrocardiograms were recorded at a paper speed of 25 mm/s and a voltage of 10 mm/mV, using a MAC VU electrocardiograph (Marquette Medical Systems, Milwaukee, Wisconsin) at these time points, and QRS duration was measured. For all patients, echocardiography was performed before and 3 and 6 months after CRT to assess LVEF, mitral regurgitation (MR) and left ventricular end diastolic diameter (LVEDD).

Two-dimensional echocardiography:

Patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed System FiVe/Seven, GE-Vingmed Ultrasound AS, Horten, Norway). Images were obtained using a 3.5-MHz transducer at a depth of 16 cm in the parasternal and apical views (standard long-axis and 2- and 4-chamber images). The LVEFs were calculated from the conventional apical 2- and 4-chamber images using Simpson's biplane technique [16]. Mitral regurgitation was characterized as: mild = 1 + (jet area/left atrial area <10%), moderate = 2 + (jet area/left atrial area 10% to 20%), moderately severe = 3 + (jet area/left atrial area 20% to 45%), and severe = 4+ (jet area/left atrial area >45%) [17]. End-diastole was identified by the onset of the R-wave on the simultaneously recorded electrocardiogram. LV dimensions were measured by a two-dimensional guided M-mode method.

Cardiac resynchronization:

Implantation was performed according to the standard technique for biventricular pacing (InSync III, Medtronic Inc., Minneapolis, MN, USA or Insyc Marquis, Medtronic Inc., Minneapolis, MN, USA), by insertion of a catheter for left ventricular (LV) stimulation in the coronary sinus, preferably in a lateral or postero-lateral branch. An atrial lead was implanted in the right atrial appendage in patients who were not in permanent atrial fibrillation. After implantation, the atrioventricular interval was optimized for maximal diastolic filling using Doppler echocardiography. Patients were discharged on the pharmacological regimen already instituted before the implant.

Statistical analysis and ethical consideration:

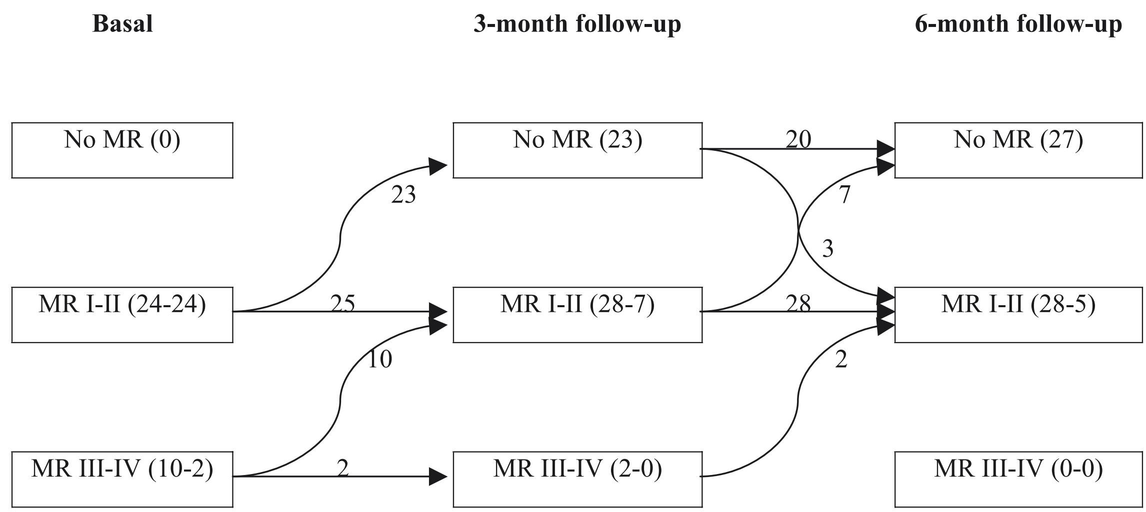
Statistical studies were carried out using the SPSS program (version 11.5, SPSS, Chicago, Illinois, USA). Quantitative data were expressed as mean ± SE. Tests such as the paired t test and Wilcoxon test were used in the analysis. For all tests, a p value <0.05 was considered significant. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

RESULTS

Patient population:

A total of 65 consecutive patients were included, with 32 (53%) having NIC and 28 (47%) IC. The study population comprised 46 men and 14 women, with a mean age of 59.5±1.3 years. According to the inclusion criteria, all patients

Figure 1. **Changes in MR scores after 3 and 6-month follow-ups.**



had a wide QRS complex (144±2 ms, range 120 to 160) and left bundle branch block configuration. Mean MR score was 1.83±0.11. The mean NYHA class was 3.1±0.05, with most patients (85%) in NYHA class III. Mean LVEF and LVEDD were 21±1%, range 10 to 35% and 6.8±0.08 mm, range 5.8 to 8.6 mm respectively. Twelve patients (20%) had severe (grade 3 and 4) MR at baseline and 48 patients (80%) had grade 1 to 2 MR (*Tab. 1*).

Three-month follow-up clinical evaluation:

Following the 3-month follow-up, MR score (mean difference: 1.05±0.10, p<0.001), NYHA class (mean difference: 0.84±0.07, p <0.001), QRS duration (mean difference: 49±3 ms, p<0.001), LVEF (mean difference: 6.2±1%, p <0.001) and also LVEDD (mean difference: 0.24±0.04 mm, p<0.001) improved significantly (*Tab. 1*). Two patients (3.3%) had severe (grade 3 and 4) MR and 35 patients (58.3%) had grade 1 to 2 MR. After 3 months of CRT implantation MR improved by at least one grade in 46 patients among 60 with basal MR (77%) (*Fig. 1*).

Six-month follow-up clinical evaluation:

Following the 6-month follow-up, NYHA class (mean difference: 1.3±0.08, p<0.001), QRS duration (mean difference: 63±2 ms, p<0.001), LVEF (mean difference: 16±1%, p <0.001) and also LVEDD (mean difference: 0.83±0.09 mm, p<0.001) improved significantly relative to the 3-month follow-up results while MR score (mean difference: 0.1±0.02) did not change significantly (*Tab. 1*). No patients had severe (grade 3 and 4) MR and 33 patients (55%) had grade 1 to 2 MR. After 6 months of CRT implantation MR improved by at least one grade in 47 patients among 60 with basal MR (78%). This improvement was detected in 16 patients among 46 patients with MR at the 3-month follow-up (43%) (*Fig. 1*). MR did not improve significantly between the 3 and 6-month evaluations, but NYHA class, QRS duration, LVEF and LVEDD improved significantly (p<0.001) (*Tab. 1*).

DISCUSSION

This longitudinal investigation demonstrated that MR improved in patients with moderate to severe heart failure after CRT implantation in evaluations performed at a 3-month follow-up. We found that this early improvement was parallel to improvements in NYHA class, QRS duration, LVEF and LVEDD. This was in contrast to the finding that MR did not change after the 3-month follow-up while improvement in other mentioned parameters continued to take place between the 3 and 6-month follow-ups. This finding was in line with previous assessments evaluating MR changes after CRT implantation [1,11-14]. The improvement in MR induced by CRT has been related both to the enhancement of the closure force and to the reduction of the tethering force that act on the mitral valve leaflets, respectively by increasing the maximal rate of left ventricular systolic pressure rise (LVCdP/dtmax) and by inducing a reversal of the ventricular remodeling [11,12].

We also compared our patients` MR scores calculated 3 months and 6 months after CRT implantation. This showed that after CRT implantation MR did not improve or aggravated significantly between 3 and 6 months after CRT implantation in patients with heart failure. Our analysis demonstrated that between these time points; NYHA class, QRS duration, LVEF and LVEDD improved significantly. This shows that the greatest part of MR improvement following CRT occurs at an early stage (within 3 months) after implantation in patients with moderate to severe heart failure, while other clinical, electrocardiographic and echocardiographic parameters continued to improve between 3 and 6 months of follow-up. This shows that MR changes cannot explain improvements in NYHA class, QRS duration, LV systolic function and size occurring between 3 and 6 months after CRT implantation. Cessation of long-term biventricular pacemaker has been shown to worsen LV systolic performance and increase functional mitral regurgitation [18]. This may be consistent with our findings indicating that medium-term CRT benefit to MR is sustained.

Although a review of the literature indicates that this is the first investigation to focus on the pattern of MR changes after CRT implantation, more evaluations with larger sample sizes and longer follow-ups seem to be necessary. Our small sample size restricted subgroup analysis (IC vs. NIC) in this study. Also in this investigation we only calculated the MR scores of our patients. For future assessments, it would seem to be of interest to consider other echocardiographic characteristics which may be related to the presence of MR in patients with heart failure. This may provide not only a better illustration of the pattern of MR-related echocardiographic changes during the post-CRT period, but also a better understanding of the mechanisms underlying MR in patients with heart failure.

CONCLUSION

MR was found to improve in an early period (during the first 3 months) after CRT implantation, and this improvement was sustained at the 6-month follow-up. Improvements in NYHA class, QRS duration, LV systolic function and size occurring between 3 and 6 months after CRT implantation cannot be explained by MR changes, which are not significant during that time.

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