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Mechanism of improvement in mitral regurgitation after cardiac resynchronization therapy

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Aims The aim of the current study was to evaluate the relationship between the presence of left ventricular (LV) dyssynchrony at baseline and acute vs. late improvement in mitral regurgitation (MR) after cardiac resynchronization therapy (CRT).

Methods and results Sixty eight patients consecutive (LV ejection fraction 23 ± 8%) with at least moderate MR (≥grade 2+) were included. Echocardiography was performed at baseline, 1 day after CRT initiation and at 6 months follow-up. Speckle tracking radial strain was used to assess LV dyssynchrony at baseline. The majority of patients improved in MR after CRT, with 43% improving immediately after CRT, and 20% improving late (after 6 months) after CRT. Early and late responders had similar extent of LV dyssynchrony (209 ± 115 ms vs. 190 ± 118 ms, P = NS); however, the site of latest activation in early responders was mostly inferior or posterior (adjacent to the posterior papillary muscle), whereas the lateral wall was the latest activated segment in late responders.

Conclusion Current data suggest that the presence of baseline LV dyssynchrony is related to improvement in MR after CRT. LV dyssynchrony involving the posterior papillary muscle may lead to an immediate reduction in MR, whereas LV dyssynchrony in the lateral wall resulted in late response to CRT.

Keywords Cardiac resynchronization therapy • Mitral valve regurgitation • LV dyssynchrony • Echocardiography • Heart failure

Introduction

Mitral regurgitation (MR) is a common finding in patients with dilated cardiomyopathy and depressed left ventricular (LV) function. Progressive remodelling and dilation of the LV may lead to annular enlargement and papillary muscle displacement resulting in functional MR.

Since the number of these patients is increasing rapidly and the presence of MR is associated with reduced survival,[1–3] treatment of MR is an important issue. Recent studies have demonstrated that cardiac resynchronization therapy (CRT) may result in improvement in MR.[4–6] However, the mechanism of this improvement in MR following CRT is not yet fully understood. LV dyssynchrony involving the posterior mitral leaflet appeared to be a determinant for the presence of MR.[7] In addition, preliminary data suggested that CRT can acutely reduce MR in patients with dyssynchrony between the papillary muscles.[8] Besides the acute effect, reduction in MR has also been shown at long-term follow-up after CRT, and is most likely secondary to LV reverse remodelling.[9,10]

In this context, we assumed that patients with late activation (dyssynchrony) of the myocardial segments adjacent to posterior

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papillary muscle will respond acutely in MR after CRT initiation, whereas patients with late activation (dyssynchrony) of the lateral LV segments will show late improvement in MR due to LV reverse remodelling. Lastly, patients without dyssynchrony will show neither an acute or chronic improvement in MR nor reverse remodelling. To evaluate the role of dyssynchrony in reduction of MR, we evaluated 68 consecutive patients with at least moderate MR who underwent CRT. Transthoracic echocardiography was used to assess indices of MR, and off-line analysis with speckle tracking radial strain was used to assess LV dyssynchrony.

Methods

Patients

Between January 2005 and September 2006, 68 patients with at least moderate MR (≥grade 2+) were selected from 206 patients eligible for CRT in Leiden University Medical Center. Eligibility for CRT was based on the current guidelines; moderate to severe heart failure [New York Heart Association (NYHA) class III or IV], depressed LV function (LV ejection fraction <35%) and wide QRS complex (≥120 ms).[11] Twenty-five patients were included in a previous paper.[8] Patients with a recent myocardial infarction (<3 months), previous mitral valve surgery, or decompensated heart failure were excluded. Etiology was considered ischaemic in the presence of significant coronary artery disease (≥50% stenosis in one or more of the major epicardial coronary arteries) and/or a history of myocardial infarction with electrocardiogram evidence, prior percutaneous coronary intervention or prior coronary artery bypass graft.

Study protocol

Clinical status was assessed at baseline and after 6 months follow-up, including assessment of NYHA class, quality of life (using the Minnesota Living with Heart Failure questionnaire),[12] and evaluation of exercise capacity using the 6 min hall walk test.[13]

Echocardiography was performed at baseline, the day after implantation and at 6-months follow-up.

Echocardiographical evaluation

All patients underwent standard transthoracic 2D echocardiography, including quantification of MR, LV function, global and local LV remodelling, and mitral valve deformation. All measurements were performed the day before implantation (*PRE*), the day after implantation (*POST*), and after 6 months of CRT (*6 MO*). Measurements of dyssynchrony were only performed at baseline. Patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed Vivid Seven, General Electric-Vingmed, Milwaukee, Wisconsin, USA). 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 6-chamber images). Standard 2D and colour Doppler data, triggered to the QRS complex, were saved in cine-loop format. For each measurement, ≥3 cardiac cycles were averaged. All echocardiographic measurements were obtained by two independent observers.

The severity of MR was graded semi-quantitatively from colour-flow Doppler images using the apical four-chamber views. Left atrial (LA) and regurgitant jet area were measured by planimetry, allowing calculation of the ratio of the jet area to the LA area.[14,15] In addition, vena contracta width was measured.[16] The severity of MR was graded on a four-point scale: mild = 1+ (jet area/LA area <10%), moderate = 2+ (jet area/LA area 10–20%, vena contracta <0.3 cm), 3+ = moderately severe (jet area/LA area 20–45%, vena contracta 0.3–0.7 cm), 4+ = severe (jet area/LA area >45%, vena contracta >0.7 cm).[17] Inter- and intraobserver agreement for jet area/LA area showed a mean value of differences respectively of 1.6% (95% limits of agreement from −7.2–10.3%) and 0.1% (95% limits of agreement −2.9–3.1%) and for vena contracta −0.03 cm (95% limits of agreement from −0.21 to 0.16 cm) and 0.01 cm (95% limits of agreement from −0.07 to 0.10 cm). The maximal rate of LV systolic pressure increase (LV d*P*/d*t*) was estimated from the steepest rising segment on the continuous wave Doppler regurgitant jet.[18]

Mitral deformation indices included valvular tenting area, coaptation height and mitral annular contraction. The valvular tenting area was obtained from the parasternal long-axis view at mid-systole and was measured as the area enclosed between the annular plane and mitral leaflets. Displacement of mitral coaptation (coaptation height) towards the LV apex was measured by the distance between leaflet coaptation and the mitral annulus plane in the apical four-chamber view. Mitral annulus diameter was measured at end-systole and end-diastole in the four-chamber view. Annular contraction was calculated as (end-diastolic diameter—end-systolic diameter) / end-diastolic diameter.[19]

LV volumes [end-diastolic volume (LVEDV), end-systolic volume (LVESV)] and LV ejection fraction were calculated from the conventional apical two- and four-chamber images, using the biplane Simpson's technique.[20] The apical displacement of posterior papillary muscle was proposed to represent the global LV remodelling and was measured as the distance between the posterior papillary muscle head and the intervalvular fibrosa (PPM-fibrosa) in the long-axis view.[19] For assessment of LA remodelling several parameters were calculated. The antero-posterior diameter was measured at end-systole on the M-mode image obtained from the parasternal long-axis view.[21] Short- and long-axis of the LA were measured on apical four-chamber views at end-systole. Furthermore, LA volumes were measured on apical two- and four-chamber views using the biplane Simpson's rule.[22,23] LA end-systolic volume (LAESV) was defined as the largest LA volume in ventricular systole; LA end-diastolic volume (LAEDV) was defined as the smallest possible LA volume in ventricular diastole.

LV dyssynchrony was calculated using speckle tracking radial strain analysis applied to baseline LV short-axis images at the papillary muscle level.[24,25] Time–strain curves for all the six segments (septal, anteroseptal, anterior, posterior, lateral, and inferior) were constructed. Peak radial strain and time from QRS onset to peak radial strain were obtained. Consequently, the location of the earliest and latest activated segments and the heterogeneity in time-to-peak radial strain for the six segments were determined.[26] LV dyssynchrony was defined as the maximal time difference between the earliest and latest activated segments; the site of latest activation was also noted (*Figure 1*). Inter- and intraobserver agreement for LV dyssynchrony showed a mean value of differences of respectively −11.5 ms (95% limits of agreement −73.5 to 50.4 ms) and 7.4 ms (95% limits of agreement from −10.7 to 25.5 ms).

Definition of response in mitral regurgitation after cardiac resynchronization therapy

At 6-month follow-up, the patients were divided into three groups based on the improvement in MR. 'Early responders' were defined as patients who improved at least one grade in MR immediately after implantation. Patients who showed an improvement of at least one grade MR after 6 months of CRT were classified as 'late responders'. 'Non-responders' showed no improvement or even deterioration in MR during follow-up.

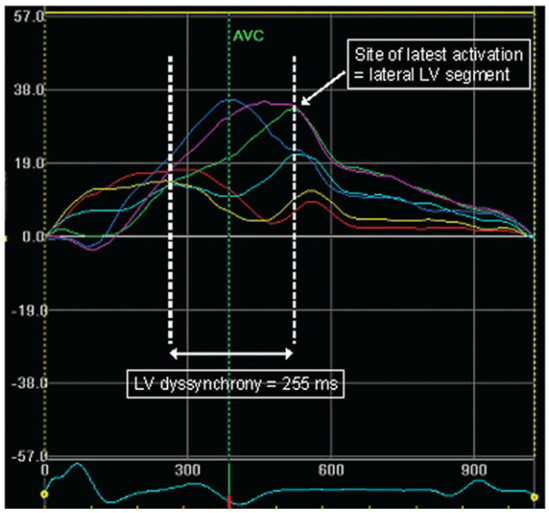

Figure 1 Time–strain curves from the mid-ventricular short-axis view for the six standard segments [yellow: antero-septal; red: anterior; green: lateral; purple: posterior; dark blue: inferior; and light blue: septal left ventricular (LV) segment]. LV dyssynchrony is present in this example as indicated by the difference in timing of peak strain between the earliest and latest activated segment of 255 ms. The latest activated segment is the lateral LV segment

Table 1 Baseline characteristics of the study population

	All patients (n = 68)
Age (years)	68 ± 9
Gender (M/F)	48/20
NYHA class (III/IV)	63/5
Ischaemic etiology	39 (57%)
QRS duration (ms)	159 ± 31
LBBB configuration	52 (76%)
SR/AF/paced	55/8/5
Grade MR (2+/3+/4+)	24/36/8
LV ejection fraction (%)	23 ± 8
LVEDV (mL)	251 ± 80
LVESV (mL)	197 ± 75
LV dyssynchrony (ms)	163 ± 120
Medication	
Anticoagulants	65 (96%)
Diuretics	63 (93%)
ACE-inhibitors	61 (90%)
Beta-blockers	52 (76%)
Spironolactone	41 (40%)

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; LBBB, left bundle branch block; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; NYHA, New York Heart Association; SR, sinus rhythm.

Cardiac resynchronization therapy implantation

A coronary sinus venogram was obtained using balloon catheter, followed by the insertion of the LV pacing lead. An 8F guiding catheter was used to position the LV lead (Easytrak 4512–80, Guidant Corporation, St Paul, MN, USA; or Attain-SD 4189, Medtronic Inc., Minneapolis, MN, USA) in the coronary sinus. The preferred position was a lateral or postero-lateral vein.[27] The right atrial and ventricular leads were positioned conventionally. All leads were connected to a dual chamber biventricular implantable cardioverter-defibrillator (Contak Renewal II or H195, Guidant Corporation; or Insync III or Insync Sentry, Medtronic Inc.).

Statistical analysis

Continuous variables are expressed as mean ± SD. Categorical data are summarized as frequencies and percentages. Inter- and intraobserver agreements for severity of MR and LV dyssynchrony parameters are calculated using Bland–Altman analysis in a subset of 20 patients. The 95% limits of agreement were defined as the range of values ± 2SDs from the mean value of differences. Patients were randomly selected and time between measurements by the same reader was >1 week. Differences in baseline characteristics between early-, late- and non-responders were analysed using one-way analysis of variance (ANOVA) with post hoc Bonferroni testing (continuous variables) and χ^2 or Fisher's exact tests (dichotomous variables) as appropriate. The relation between response-pattern and change in echocardiographic parameters over time was then studied using repeated measures two-way ANOVA. We assumed that every pair of measurements has the same correlation coefficient across subjects and that the variance and covariances are homogenous across time. This specific structure for the covariance is referred to as compound symmetry, and it is reasonable to assume such structure in view of the relatively short follow-up (6 months). The paired Students t test was used to compare continuous data within the three subgroups during follow-up. In acute responders and non-responders mitral deformation indices and parameters indicating LV function measured immediately after implant were compared with the baseline values, whereas in late responders and non-responders the 6 months follow-up measurements were compared with baseline. LA function and volumes measured at baseline and at 6 months follow-up were compared within all the three groups. To adjust for inflation of the type I error with multiple tests, we applied a Bonferroni correction; for changes in mitral deformation indices and LV function we considered a P-value of $<0.05/4$ statistically significant; for changes in LA function and volumes, a P-value of $<0.05/3$ was considered significant.

Results

Patient characteristics

Baseline characteristics of the 68 consecutive patients (48 men, age 68 ± 9 years) included in this study are summarized in *Table 1*. All patients had central jets, secondary to LV dilatation; 24 patients (35%) having moderate MR (grade 2+), 36 patients (53%) having moderately severe MR (grade 3+) and eight patients (12%) had severe MR (4+) before CRT implantation. Most patients had NYHA class III (93%) and mean LV ejection fraction was 23 ± 8%. All patients received optimized medical therapy, if tolerated. Device implantation was successful in all patients and no

procedure-related complications were observed. However, seven patients died of worsening heart failure before the 6-month follow-up evaluation.

Clinical and functional improvement after cardiac resynchronization therapy

After 6 months of CRT, 40 patients improved one NYHA class and five patients improved two NYHA classes (McNemar test, $P < 0.001$). The quality-of-life score decreased from 35 ± 18 to 22 ± 19 ($P < 0.001$). In addition, a significant increase in 6 min walking distance was noted (from 290 ± 110 m to 374 ± 127 m, $P < 0.001$).

One day after implantation, LVESV showed a modest decrease from 197 ± 95 mL to 190 ± 76 mL ($P < 0.001$) accompanied with an improvement in LV ejection fraction (from $23 \pm 8\%$ to $25 \pm 9\%$, $P < 0.001$). Significant reverse remodelling was observed at 6 months follow-up, as evidenced by a decrease in LVEDV from 251 ± 80 mL at baseline to 216 ± 89 mL ($P < 0.001$) after 6 months of CRT. Similarly, LVESV decreased from 197 ± 75 mL to 155 ± 80 mL ($P < 0.001$). Furthermore, the LV ejection fraction improved from $23 \pm 8\%$ to $30 \pm 10\%$ ($P < 0.001$).

Improvement in mitral regurgitation after cardiac resynchronization therapy

Immediately after CRT 26 patients improved one grade in MR and three patients improved two grades, resulting in 29 early responders (43%). The group of late responders comprised 14 patients (20%); 12 patients showed a reduction of one grade in MR, two patients showed a reduction of two grades after 6 months. Twenty-five patients (37%) were considered non-responders, including the patients who died before 6 months of follow-up. Early responders showed an immediate reduction in severity of MR after CRT, which was maintained or even further, reduced after 6 months of CRT (*Figure 2*, *Table 2*). In contrast, late responders exhibited reduction in MR only after 6 months of CRT. In the non-responder group, severity of MR did not change during the entire follow-up.

Regarding mitral deformation indices, *Figure 3* demonstrates significant differences in trend during follow-up between acute, late and non-responders. Acute improvement in MR was accompanied by an acute significant improvement in tenting area (from 7.8 ± 1.0 cm^2 to 7.2 ± 0.9 cm^2, $P < 0.001$), coaptation height (from 1.9 ± 0.2 cm to 1.8 ± 0.2 cm, $P < 0.001$) and mitral annular contraction (from $16 \pm 4\%$ to $20 \pm 4\%$, $P < 0.001$). This improvement was even more pronounced after 6 months of CRT. In the late responders these mitral deformation indices did not improve acutely after CRT, but did improve after 6 months (in all $P < 0.005$). Lastly, the non-responder group showed neither improvement in MR as well as in tenting area, coaptation height, and mitral annular contraction during the entire follow-up.

Furthermore, *Figure 3* also demonstrates acute local remodelling after initiation of CRT in acute responders, as demonstrated by an acute reduction in PPM-fibrosa distance from 6.7 ± 0.5 cm to 6.4 ± 0.6 cm ($P < 0.001$), with a further reduction to 6.1 ± 0.6 cm after 6 months. Local LV remodelling in late responders was noted only after 6 months (from 6.7 ± 0.7 cm to 6.2 ± 0.7 cm, $P < 0.001$). The non-responders showed no change at all in local LV remodelling. Global changes in LV function were also noted in acute responders as demonstrated by an immediate improvement in LV d*P*/d*t*, a reduction in LVESV, and consequently an improvement in LV ejection fraction (all parameters $P < 0.001$, *Table 2*). This improvement was maintained or even further improved after 6 months of CRT, with significant LV reverse remodelling. Late responders showed a reduction in LV volumes and improvement in LV function after 6 months of follow-up ($P < 0.001$). Non-responders in MR showed no improvement in indices of global LV remodelling during the entire follow-up. Of note, 72% of the early responders and 93%

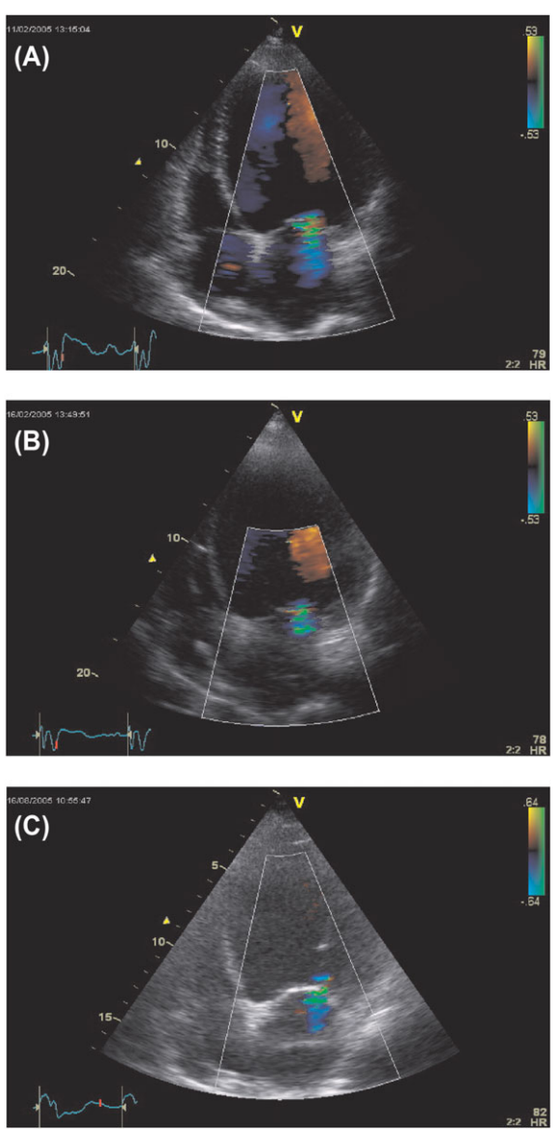

Figure 2 Colour Doppler images of an 'acute responder'. Acute reduction in mitral regurgitation is seen immediate after cardiac resynchronization therapy (*B*) compared with baseline (*A*). (*C*) Demonstrates a sustained reduction at 6-months follow-up

Table 2 **Effect of cardiac resynchronization therapy on severity of mitral regurgitation (MR) and left ventricular (LV) function and LV volumes between patients who show an acute improvement in MR (Early), a late improvement after 6 months of follow-up (Late) or no improvement at all (Non). The following comparisons were made: in early responders PRE vs. POST; in late responders PRE vs. 6 MO and in non-responders both. The corresponding *P*-values are added between brackets. To correct for repeated measurements a *P*-value of <0.013 was considered statistically significant**

		Early (n = 29)	Late (n = 14)	Non (n = 25)	*P*-value
MR (grade)	PRE	2.8 ± 0.6	2.8 ± 0.7	2.8 ± 0.7	1.0
	POST	1.7 ± 0.7 ($P < 0.001$)	2.8 ± 0.7	2.8 ± 0.7 (P = 0.7)	
	6 MO	1.6 ± 0.8	1.7 ± 0.7 ($P < 0.001$)	2.9 ± 0.8 ($P = 0.4$)	
Jet area (cm^2)	PRE	7.1 ± 3.2	7.9 ± 4.0	7.0 ± 4.7	0.7
	POST	3.5 ± 1.9 ($P < 0.001$)	7.9 ± 4.0	7.8 ± 4.2 ($P = 0.8$)	
	6 MO	3.0 ± 1.3	3.7 ± 2.1 ($P < 0.001$)	8.5 ± 4.9 ($P = 0.3$)	
Jet area/LA area (%)	PRE	34 ± 13	34 ± 15	35 ± 15	1.0
	POST	18 ± 9 ($P < 0.001$)	34 ± 15	34 ± 14 ($P = 0.3$)	
	6 MO	17 ± 8	20 ± 11 ($P < 0.001$)	35 ± 15 ($P = 0.7$)	
Vena contracta (cm)	PRE	0.46 ± 0.16	0.46 ± 0.22	0.42 ± 0.20	0.8
	POST	0.31 ± 0.12 ($P < 0.001$)	0.47 ± 0.20	0.43 ± 0.19 ($P = 0.7$)	
	6 MO	0.31 ± 0.10	0.27 ± 0.14 ($P < 0.001$)	0.44 ± 0.18 [P=0.3]	
LV d*P*/d*t* (mmHg/s)	PRE	669 ± 335	705 ± 444	702 ± 239	1.0
	POST	1134 ± 608 ($P < 0.001$)	851 ± 451	714 ± 185 ($P = 0.6$)	
	6 MO	1123 ± 605	1174 ± 496 ($P = 0.005$)	721 ± 265 ($P = 0.8$)	
LVESV (mL)	PRE	194 ± 81	191 ± 48	205 ± 82	0.8
	POST	182 ± 82 ($P < 0.001$)	187 ± 48	201 ± 81 ($P = 0.1$)	
	6 MO	142 ± 83	134 ± 50 ($P < 0.001$)	189 ± 87 ($P = 0.3$)	
LVEDV (mL)	PRE	251 ± 82	241 ± 46	256 ± 94	0.8
	POST	249 ± 83 ($P = 0.4$)	243 ± 44	259 ± 92 ($P = 0.2$)	
	6 MO	204 ± 91	195 ± 54 ($P < 0.001$)	249 ± 102 ($P = 0.9$)	
LV ejection fraction (%)	PRE	24 ± 8	22 ± 7	22 ± 8	0.5
	POST	28 ± 9 ($P < 0.001$)	24 ± 9	23 ± 8 ($P = 0.1$)	
	6 MO	33 ± 10	33 ± 9 ($P < 0.001$)	25 ± 8 (P = 0.1)	

LA, left atrial; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume.

of the late responders showed >15% reduction in LVESV after 6 months as compared with only four patients (20%) in the non-responder group ($P < 0.001$).

LA remodelling was only assessed at 6 months follow-up (*Table 3*). LA diameters showed a significant reduction during follow-up in early responders ($P < 0.001$) with a trend for reduction in late responders ($P = 0.034$ for LA LAX and $P = 0.040$ for LA SAX). LA volumes, however, were significantly decreased. Non-responders showed no LA reverse remodelling.

Left ventricular dyssynchrony and improvement in mitral regurgitation

As demonstrated in *Table 4*, baseline characteristics of all three patient groups were similar except for the indices of LV dyssynchrony at baseline. Of note, speckle tracking analysis was possible in all but three patients due to technically inadequate short-axis images and 18 segments (5%) of the remaining 390 segments had to be eliminated because of negative strain values.

Non-responders showed less LV dyssynchrony at baseline compared with early and late responders (99 ± 74 ms vs. 209 ± 115 ms vs. 190 ± 118 ms, $P < 0.001$). Early and late responders had similar extent of LV dyssynchrony; however, the site of latest activation in early responders was the posterior or the inferior LV segment, which is adjacent to the posterior papillary muscle, whereas in late responders the site of latest activation was the lateral LV segment (*Figure 4*).

In contrast, evaluation of 100 random CRT candidates without (34%) or mild MR (grade 1+, 66%) demonstrated similar extent of LV dyssynchrony as compared with patients with at least moderate MR (167 ± 122 ms vs. 163 ± 120 ms, $P = 0.8$). However, different distribution of site of latest activation was noted (*Figure 5*), with the lateral segment contracting latest in the majority of patients. Interestingly, only 18% of the patients demonstrated late contraction of the posterior and inferior segments.

Discussion

The results of the current study can be summarized as follows: (i) the majority of patients included in this study improved in MR after CRT, with 43% improving immediately after CRT, and 20%

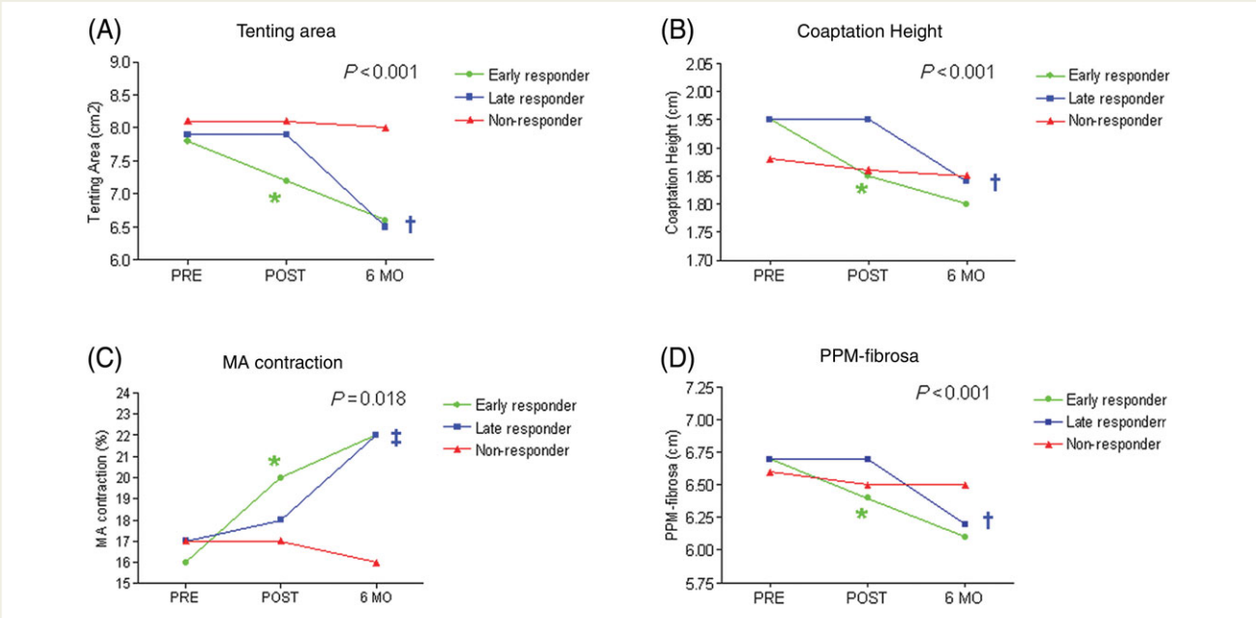

Figure 3 Effects of cardiac resynchronization therapy on mitral deformation indices (*A*–*C*) and global left ventricular remodelling (*D*) immediately after implantation (POST) and after 6 months (6 MO). Patients are grouped into early, late and non-responders according to the improvement in their mitral regurgitation. The *P*-value indicates a significant difference in trend during follow-up between the three groups. (Asterisk: PRE vs. POST $P < 0.001$; dagger: PRE vs. 6 MO $P < 0.001$; double dagger PRE vs. 6 MO $P < 0.005$)

Table 3 Effect of cardiac resynchronization therapy (CRT) on left atrial size and volumes between patients who show an acute improvement in mitral regurgitation (MR) (Early), a late improvement after 6 months of follow-up (Late) or no improvement at all (Non)

		Early ($n = 29$)	Late ($n = 14$)	Non ($n = 25$)	*P*-value
LA diameter (cm)	PRE	4.7 ± 0.7	4.8 ± 0.8	4.9 ± 0.8	0.7
	6 MO	4.3 ± 0.8[a]	4.5 ± 0.8[a]	4.8 ± 0.9	
LA LAX (cm)	PRE	5.2 ± 0.4	5.3 ± 0.7	5.3 ± 1.1	0.8
	6 MO	4.8 ± 0.6[a]	5.0 ± 0.6	5.2 ± 0.9	
LA SAX (cm)	PRE	4.5 ± 0.6	4.4 ± 0.7	4.2 ± 0.9	0.9
	6 MO	3.9 ± 0.8[a]	4.0 ± 0.8	4.2 ± 0.9	
LAESV (mL)	PRE	63 ± 21	70 ± 23	66 ± 29	0.6
	6 MO	53 ± 22[a]	60 ± 23[a]	69 ± 31	
LAEDV (mL)	PRE	49 ± 17	50 ± 20	48 ± 28	1.0
	6 MO	41 ± 17[a]	40 ± 21[a]	48 ± 34	

LA, left atrium; LAESV, left atrial end-systolic volume; LAEDV, left atrial end-diastolic volume; LAX, long-axis; SAX, short-axis.
[a]PRE vs. 6 MO $P < 0.001$.

improving late (at 6 months) after CRT; (ii) the site of latest activation (the most dyssynchronous region) in early responders was mostly posterior or inferior (close to the posterior papillary muscle), whereas the lateral wall was the latest activated segment in late responders; (iii) improvement in MR was accompanied by an improvement in mitral deformation indices, as well as in global and local LV reverse remodelling as in LA remodelling.

Mechanism of mitral regurgitation in dilated cardiomyopathy

The development of functional MR in dilated cardiomyopathy has been attributed to annular enlargement secondary to the LV dilatation and papillary muscle displacement due to LV remodelling, which results in tethering and mitral valve tenting.[28,29] Boltwood *et al.*[30] have reported that annular dilatation is the main

Table 4 Baseline characteristics in patients who show an acute improvement in mitral regurgitation after cardiac resynchronization therapy (Early), a late improvement after 6 months of follow-up (Late) or no improvement at all (Non)

	Early ($n = 29$)	Late ($n = 14$)	Non ($n = 25$)	*P*-value
Age (years)	68 ± 10	71 ± 7	66 ± 8	0.3
Gender (M/F)	19/10	10/4	19/6	0.7
NYHA class (III/IV)	28/1	13/1	22/3	0.5
Ischaemic etiology	19 (56%)	6 (43%)	14 (56%)	0.4
QRS duration (ms)	157 ± 29	175 ± 33	153 ± 31	0.1
LBBB configuration	22 (76%)	10 (71%)	20 (80%)	0.3
SR/AF/Paced	25/1/3	10/2/2	20/5/0	0.4
Grade MR (2+/3+/4+)	9/18/2	5/7/2	11/12/4	0.7
LV ejection fraction (%)	24 ± 8	22 ± 7	22 ± 8	0.5
LVEDV (mL)	251 ± 82	241 ± 46	256 ± 94	0.8
LVESV (mL)	194 ± 81	191 ± 48	205 ± 82	0.8
LV dyssynchrony (ms)	209 ± 115	190 ± 118	99 ± 74	<0.001

AF, atrial fibrillation; LBBB, left bundle branch block; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; NYHA, New York Heart Association; SR, sinus rhythm.

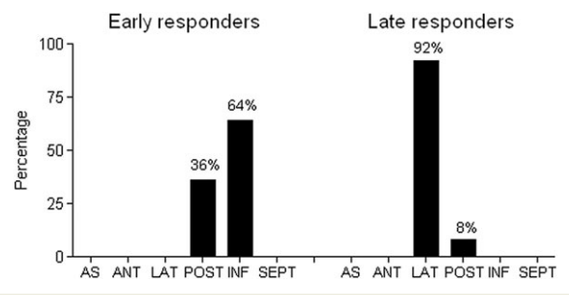

Figure 4 Distribution of site of latest activation between early and late responders in improvement in mitral regurgitation after cardiac resynchronization therapy (AS: antero-septal; ANT: anterior; LAT: lateral, POST: posterior, INF: inferior, SEPT: septal LV segment)

determinant of MR in patients with dilated cardiomyopathy. Other studies have demonstrated that systolic mitral valve tenting is the main determinant of mitral valve incompetence.[28,29,31] Lancellotti *et al.*[19] demonstrated in 70 ischaemic patients that severity of MR at rest best correlated with changes in mitral deformation (tenting area, coaptation height) during exercise. Moreover, posterior displacement of the papillary muscle was associated with severity of MR.

The presence of LV dyssynchrony may also contribute to MR. LV dyssynchrony decreases LV contraction efficiency and closing

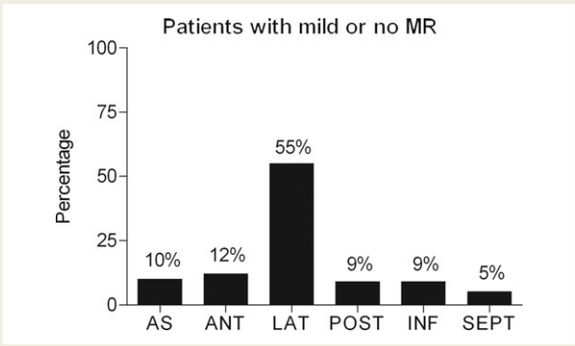

Figure 5 Distribution of site of latest activation in 100 cardiac resynchronization therapy patients without significant mitral regurgitation (MR) at baseline (AS: antero-septal; ANT: anterior; LAT: lateral, POST: posterior, INF: inferior, SEPT: septal LV segment)

forces thereby impairing mitral valve tenting.[4] Moreover, dyssynchrony between the LV segments supporting the papillary muscles produces uncoordinated regional LV mechanical activation in these segments, resulting in geometric changes in mitral leaflet attachments and implying tethering of the mitral leaflets.[5] For instance, in previous work we measured a time delay of 169 ± 69 ms between maximal contraction of the anterior papillary muscle and the posterior papillary muscle in 25 patients with moderate-severe MR.[8]

Acute vs. late improvement in mitral regurgitation

CRT has been reported to reduce MR. However, some patients exhibit immediate reduction in MR, whereas other patients show improvement only late after CRT. Indeed, several acute CRT studies reported an acute MR reduction.[4–6] For instance, Lancellotti and coworkers studied 27 patients (LV ejection fraction 29 ± 5%) with CRT on and off, and demonstrated that MR improved immediately after CRT, with a reduction in effective regurgitant orifice area from 22 ± 10 mm^2 to 13 ± 7 mm.[2,6] Furthermore, these changes in MR were directly related to changes in LV systolic function (LV d*P*/d*t*). The likely cause of the improvement in MR was concluded to be a decrease in LVESV and coordination of ventricular contraction, leading to restoration of mitral valve closure. Kanzaki *et al.*[5] noted a similar reduction in MR severity and added the role of papillary muscle resynchronization during CRT. Along with the reduction in MR severity, the inter-papillary muscle time delay shortened from 106 ± 74 ms at baseline to 39 ± 43 ms after CRT ($P < 0.001$). Furthermore, the change in inter-papillary muscle time delay correlated well with the decrease in MR severity after CRT ($r = 0.77$, $P < 0.001$). Similar results from our group concerning the mechanism of acute reduction in MR after CRT were reported recently.[8] At baseline, a time delay of 169 ± 69 ms between the anterior and the posterior papillary muscle was present, that decreased immediately to 25 ± 46 ms after CRT along with a reduction in MR severity (evidenced by a

reduction in vena contracta width from 0.54 ± 15 cm to 0.39 ± 0.13 cm, $P < 0.001$).

Besides the acute effect of CRT on MR, reduction in MR has also been shown at long-term follow-up; data from the MIRACLE trial and other large trials have demonstrated a significant reduction in average MR jet area and MR severity after CRT.[9,10] Thus, immediate reduction in MR severity can be attributed to resynchronized papillary muscle activation and improved coordination of LV contraction, which results in improved systolic function and reduced mitral leaflet tethering forces. The likely cause of late improvement in MR is LV reverse remodelling leading to a reduction in mitral annular size, with restoration of mitral valve closure. Of note, late responders in MR also show an acute improvement in LVESV probably as a result of a decrease in LV dyssynchrony with a coordinated contraction.

The current study evaluated the different mechanisms of reduction in MR after CRT. Importantly, the majority of patients (63%) demonstrated a reduction in MR severity after CRT, either acute or late. Acute improvement in MR severity was accompanied by acute improvements in mitral deformation, LV function and LA function, which were maintained or improved even further during late follow-up. Late improvement in MR (after 6 months of CRT), was accompanied by LV reverse remodelling, global LV remodelling and improved mitral deformation indices. Interestingly, both acute and late responders exhibited severe baseline LV dyssynchrony, but a different location of LV dyssynchrony was noted in both groups. In acute responders the inferior or posterior segments showed the latest activation, whereas in late responders the lateral wall showed the latest activation. The posterior papillary muscles are located adjacent to the inferior or posterior LV segments, suggesting involvement of the papillary muscle in the dyssynchrony in acute responders. This hypothesis is further supported by the fact that patients without significant MR have similar extent of LV dyssynchrony but show less often a posterior or inferior site of latest activation. Future larger studies are warranted to further elucidate the role of dyssynchrony in functional MR.

Conclusions

The observations in the present study indicate that the improvement in MR after CRT is related to the presence of LV dyssynchrony. If the LV dyssynchrony involves the posterior papillary muscle an immediate reduction in MR can be expected after CRT (secondary to resynchronization of the posterior papillary muscle), whereas in patients with LV dyssynchrony not involving the posterior papillary muscle late improvement in MR can be expected (related to LV reverse remodelling with subsequent reduction in mitral annular size and improved closure of the valve).

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