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Effects of cardiac resynchronization therapy on the mechanisms underlying functional mitral regurgitation in congestive heart failure

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Abstract *Aims:* Functional mitral regurgitation (FMR) improvement induced by cardiac resynchronization therapy (CRT) has been related to left ventricular (LV) remodeling reversal and contractility enhancement. The effects induced by the changes of LV synchronicity indexes on FMR severity have not been investigated.
Methods and results: In 30 patients with CRT for heart failure (HF) and QRS $>$ 130 ms, LV function parameters, FMR severity as mitral jet regurgitation/left atrial area ratio (JA/LAA) and standard deviation (SD) of the time to the systolic peak velocity at 6-basal and mid-LV segments as asynchrony indexes were evaluated (echo/tissue Doppler) before and 6 months after implant. At follow-up, 15 patients resulted responders to LV reverse remodeling with $\geq$15% end-systolic volume (ESV) and LV systolic function improvement. Improvement of FMR with $\geq$15% JA/LAA reduction was observed in 19 patients, 7 were nonresponders to LV reverse remodeling. In patients with $\geq$15% JA/LAA reduction a significant decrease of LV asynchrony indexes was observed as compared to patients without $\geq$15% JA/LAA reduction in whom LV asynchrony indexes were increased. Reduction of LV mid-segmental asynchrony was the variable most strongly related to JA/LAA reduction ($r^2 = 0.697$, $P < 0.01$), with good agreement between observed and predicted values (only 1 patient outside the mean $\pm$ 2SD).

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Conclusion: These data reveal that CRT can reduce FMR irrespective to LV remodeling reversal; this effect is related to LV asynchrony reduction and further support CRT employment in patients with HF and FMR.

Introduction

Cardiac resynchronization therapy (CRT) was shown to improve left ventricular (LV) performance, quality of life (QoL), exercise tolerance, hospitalization and survival rate in patients with dilated cardiomyopathies and left ventricular conduction abnormalities.[1–5] Recently some studies focused on potential of CRT to reverse LV remodeling and to block the vicious circle that contributes to progression and auto maintaining of heart failure.[6–8] Moreover, there is evidence that in the same time CRT improves functional mitral regurgitation (FMR) that in turn contributes to further reverse ventricular remodeling.[9,10] FMR is a common finding in heart failure (HF) patients with higher prevalence and severity in the more symptomatic patients.[11] It has important prognostic implications since the presence of moderate to severe mitral regurgitation is associated with a higher mortality rate.[11] Experimental and clinical studies demonstrated that FMR results from an imbalance between the closing and the tethering forces that act on the mitral valve leaflets.[12–14] The improvement of FMR induced by CRT has been related both to the enhancement of the closure force, by increasing the maximal rate of left ventricular systolic pressure rise ($LV + dP/dt_{max}$), and to the reduction of the tethering force by inducing a reversal of the ventricular remodeling.[7,10] However, little is known about the effects induced by the changes of LV synchronicity indexes on FMR severity.

The aim of our study was to investigate the relationship between the restored LV systolic synchronicity and the reduction of FMR.

Methods

Patients

Thirty patients in New York Heart Association (NYHA) class III–IV HF, LV ejection fraction $< 35\%$ and prolonged QRS (> 130 ms), received biventricular pacing therapy. Clinical and demographic variables are reported in Table 1: in 14 patients (46.7%) the aetiology of HF was ischemic and nonischemic in 16 patients (53.3%). Medications included diuretics in 80% of patients, ACE-inhibitors in 82%, beta-blockers in 78%, spironolactone in 15%, and digoxin in 30%. These patients were treated with maximal tolerable doses of HF medications and remained clinically stable for ≥ 1 month before enrollement. All patients were in sinus rhythm.

Protocol

Investigations were performed before (at baseline) and 6 months after biventricular pacemaker implantation. They included echocardiography, QoL evaluated by Minnesota Living with Heart Failure questionnaire and NYHA class. The study was approved by the Institutional Review Board and witnessed informed consent was obtained by which patient.

Biventricular pacemaker implantation

Three transvenous pacing leads were inserted, one in the right atrium and another on the high interventricular septum or in the right ventricular outflow tract. In addition, a coronary sinus lead was positioned on the LV free wall through a coronary sinus tributary. The location of the LV pacing lead was in the lateral vein in 70% and in

Table 1 Baseline clinical characteristics of all patients

Age (years)	73.7 ± 6.3
Sex (male/female, *n*)	28/2
NYHA class	3.03 ± 0.3
WCT (*m*)	334.9 ± 154.9
QoL (score)	28.4 ± 16.1
QRS duration (ms)	140 ± 10
IHD/non-IHD (*n*)	14/16
Diuretics *n* (%)	24 (80)
Beta-blockers *n* (%)	23 (78)
Spironolactone *n* (%)	5 (15)
Digoxin *n* (%)	9 (30)
ACE-inhibitor *n* (%)	25 (82)

Data are presented as the mean value $\pm$ SD, number or percentage of patients. ACE = angiotensin-converting enzyme; IHD = ischemic heart disease; NYHA = New York Heart Association; QoL = quality of life; WCT = Walk corridor test.

the posterolateral vein the remaining 30%. The biventricular devices used were InSynch (Medtronic Inc., Minneapolis, Minnesota) in 14 patients, and Contak TR CHFD (Guidant Inc., St. Paul, Minnesota) in 16 patients.

After implantation the atrioventricular interval was optimized for maximal diastolic filling using Doppler echocardiography.

Echocardiography

Standard echocardiography, including Doppler studies, was performed using a Vivid 7 System (Vingmed-General Electric, Horten, Norway). The following parameters were evaluated: LV end-diastolic and end-systolic volume (EDV and ESV, respectively), ejection fraction (EF) as $EDV - ESV/EDV \times 100$, left atrial area (LAA) evaluated from the apical 4-chamber view at the end of systole, myocardial performance index (MPI) calculated as the sum of isovolumetric contraction and relaxation times divided by ejection time,[15] peak flow velocity in early diastole (E), peak flow velocity in late diastole during atrial contraction (A) and E/A ratio, sphericity index (Sph. Ind.), as EDV divided by the volume of a sphere whose diameter was the major end-diastolic LV long axis (the LV long axis was obtained as the longest distance between the centre of the mitral annulus and the endocardial apex), mitral annulus area deformation (MAAdef) evaluated as diastolic mitral annulus area minus systolic mitral annulus area divided by diastolic mitral annulus area percent. The mitral annulus systolic and diastolic area were calculated using $\pi(a/2)(b/2)$ formula for an ellipse with a diameter measured in the 4-chamber view and b diameter measured in the 2-chamber view[16]; the severity of mitral regurgitation was assessed by the percent jet area (JA) relative to left atrial size in the apical 4-chamber view (JA/LAA)[17] and by the evaluation of the effective regurgitant orifice area (EROA), calculated by the proximal isovelocity surface area method: $EROA = 2\pi r^2 V_N/V_R$, where $2\pi r^2$ = area of a hemispheric shell derived from the radius (r), V_N = aliased velocity identified as the Nyquist limit and V_R = peak regurgitant velocity. The proximal isovelocity surface area radius was measured as the distance from the first alias to a point at the trailing edge of the mitral leaflets nearest the regurgitant orifice along a vector parallel to the direction of interrogation at a point in mid-systole,[18] LV rate of pressure rise in systole ($+dP/dt_{max}$) estimated from the continuous-wave Doppler mitral regurgitation velocity curve.[19]

The interventricular electromechanical delay (IVD) was also calculated as the time difference between the aortic and pulmonary pre-ejection time intervals where aortic and pulmonary ejection flows were recorded, respectively, in the 4-chamber apical and parasternal views. The aortic pre-ejection time interval was defined as the time duration between the QRS onset on the surface ECG and the onset of the aortic ejection flow, whereas the pulmonary pre-ejection time interval was defined as the time duration between the QRS onset on the surface ECG and the onset of the pulmonary ejection flow.

Two-dimension echocardiography with tissue Doppler-colour imaging (TDI) was performed with a 2.5- or 3.5-MHz phase array transducer for the long axis motion of the ventricles. Gain setting, filters, and pulse repetition frequency were adjusted to optimize colour saturation, and sector size and depth were optimized for the highest frame rate. At least 3 consecutive beats were stored and the images were digitized and computer analyzed offline (EchoPac 6.3.6, Vingmed-General Electric, Horten, Norway). Myocardial pulse-Doppler velocity profile signals were reconstituted offline from the TDI colour images that provided regional myocardial velocity curves.

From the apical 4-chamber view, 2-chamber and long axis views, a 6-basal and 6-mid-segmental model were obtained in the LV, namely the septal, lateral, anteroseptal, posterior, anterior, and inferior segments at both basal and mid-levels. The time to the systolic peak velocity (T_S) was measured in every segment. For the T_S, the beginning of the QRS complex was used as the reference point. Standard deviation of T_S was assumed as LV asynchrony index as proposed by Yu et al.[20] and evaluated globally in all 12 LV segments and separately in the 6-basal and 6-mid-LV segments. Global, basal and mid-LV asynchrony indexes were obtained namely Asynch. $Ind._G$, Asynch. $Ind._B$ and Asynch. $Ind._M$, respectively (Fig. 1a,b). Recently a simple method for identification of LV dyssynchrony has been proposed by Bax et al., based on evaluation of the maximum delay between 4 basal segments derived from the 2- and 4-chamber images.[21] We evaluated the delay at 6 basal and mid-LV segments using all the three apical chamber views in order to better investigate the effects of CRT on mitral valve apparatus efficiency.

Statistical analysis

For the comparison of parametric variables before and after CRT, paired-sample t-test was used. The comparison of clinical and echocardiographic parameters between responder and

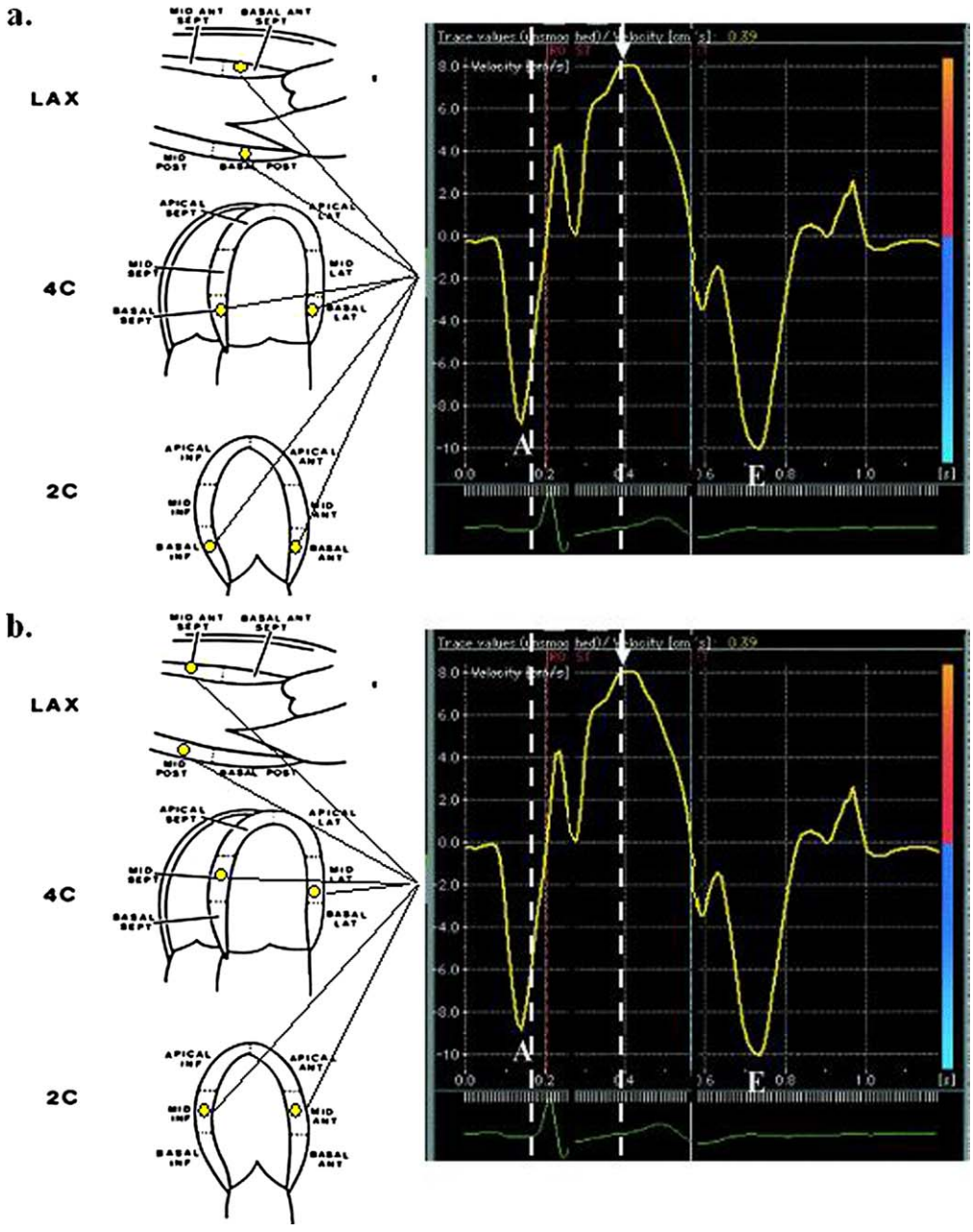

Figure 1 Schematic representation of the method to evaluate the left ventricular asynchrony indexes by using tissue Doppler imaging. Regional myocardial velocity curves were reconstituted offline from the TDI colour imaging from the apical 4-chamber (4C) view, 2 chamber (2C) and long axis (LAX) views; a 6-basal and 6-mid-segmental model were obtained in the LV, namely the septal, lateral, anteroseptal, posterior, anterior, and inferior segments at both basal and mid-levels. The time to the systolic peak velocity (T_S) was measured in every segment using the beginning of QRS as the reference point. In (a) SD of T_S is evaluated at 6 basal LV segments and assumed as index of basal LV asynchrony (Asynch. Ind.$_B$). In (b) SD of T_S is evaluated at 6 mid-LV segments and assumed as mid-LV asynchrony index (Asynch. Ind.$_M$). SD of T_S evaluated at both 6 basal and 6 mid-LV segments is assumed as index of global LV asynchrony (Asynch. Ind.$_G$).

nonresponders groups was performed by unpaired *t*-test. Regression analysis was used to compare the relationship between the percent changes of all echocardiographic parameters evaluated and the changes of JA/LAA ratio in univariate model, followed by multivariate analysis in a stepwise multiple regression model. Bland and Altman statistic was then performed in order to assess the agreement between the found and the predicted JA/LAA change. All data are expressed as mean $\pm$ SD. A probability value < 0.05 was considered statistically significant.

Results

At 6-month follow-up, patients were divided into responders and nonresponders based on LVESV reduction by $\geq$15%.[22] Among the 30 patients, there were 15 responders to reverse remodeling with reduction in LVESV of $\geq$15% and 15 nonresponders in whom reduction in LVESV was $<$15%. Ischemic heart disease (IHD) was present in 40% of the responders and in 33% of the nonresponders. At baseline NYHA class, QoL and all ecocardiographic parameters evaluated were similar in the two groups except for EF ($P < 0.05$) that was significantly lower in responders than in nonresponders and for Asynch. Ind.$_G$ ($P < 0.05$), that was higher in responder group (Table 2).

At follow-up, in responders to $\geq$15% LVESV reduction, NYHA class ($P < 0.05$), QoL ($P < 0.05$) were significantly improved. LVEDV and LVESV ($P < 0.0001$) were significantly reduced, with significant improvement in EF ($P < 0.0001$), LV + dP/dt_{max} ($P < 0.01$), MPI ($P < 0.001$) and Sph. Ind. ($P < 0.05$), indicating that a reversal of ventricular remodeling had been achieved although the diastolic parameters (E, A, E/A) and LAA were unchanged. JA/LAA ratio was significantly reduced ($P < 0.05$) while EROA reduction was not significant; however, due to technical problems, its measurement was performed only in 20 patients.

These changes were associated with interventricular and intraventricular resynchronization as indicated by the significant reduction of IVD ($P < 0.05$), Asynch. Ind.$_G$ ($P < 0.05$), Asynch. Ind.$_B$ ($P < 0.05$), and Asynch. Ind.$_M$ ($P < 0.05$) (Table 2).

In nonresponders to LV reverse remodeling, NYHA class was unchanged, while improvement of QoL was observed ($P < 0.05$). All LV asynchrony indexes were unchanged although IVD was significantly reduced ($P < 0.05$). LVEDV ($P < 0.05$), LVESV ($P < 0.05$) were significantly increased, with a significant reduction in EF ($P < 0.05$). Worsening of diastolic parameters that shifted toward a

Table 2 Clinical and echocardiographic effects of CRT in responders and nonresponders to LV reverse remodeling

	Responders ($n = 15$)		Nonresponders ($n = 15$)	
	Baseline	Follow-up	Baseline	Follow-up
NYHA class	3.2 ± 0.7	1.9 ± 0.3†	3 ± 1	2.2 ± 0.8
QoL (score)	29 ± 14	12 ± 9†	30 ± 11	19 ± 14$^{\|}$
EF (%)	24 ± 7	39 ± 10§	30 ± 8*	27 ± 7$^{\|}$
LVEDV (ml)	284 ± 87	213 ± 65§	252 ± 89	279 ± 113$^{\|}$
LVESV (ml)	220 ± 74	135 ± 55§	178 ± 70	207 ± 94$^{\|}$
MPI	1.1 ± 0.3	0.7 ± 0.3**	1.1 ± 0.3	1 ± 0.3
LV + dP/dt_{max} (mmHg/s)	537 ± 188	1082 ± 512‡	509 ± 339	634 ± 182
E (cm/s)	64 ± 29	68 ± 34	81 ± 29	84 ± 24
A (cm/s)	65 ± 32	64 ± 34	65 ± 31	48 ± 18$^{\|}$
E/A	1.2 ± 1	1.4 ± 1.1	1.6 ± 1.3	2 ± 1.2$^{\|}$
Sph. Ind.	0.6 ± 0.1	0.5 ± 0.1†	0.6 ± 0.1	0.6 ± 0.1
MAAdef (%)	19 ± 10	25 ± 8	22 ± 9	22 ± 9
LAA (cm^2)	24 ± 6	24 ± 6	27 ± 8	26 ± 8
JA (cm^2)	6.9 ± 3.8	3.7 ± 2.4‡	8.8 ± 4.4	7.2 ± 3.3
JA/LAA (%)	30 ± 19	15 ± 6†	32 ± 14	27 ± 9
Asynch. Ind.$_G$ (ms)	53.7 ± 23.3	36.4 ± 18.7†	41.0 ± 15.7*	45.9 ± 23.9
Asynch. Ind.$_B$ (ms)	40.9 ± 17.4	30.8 ± 15.6†	33.9 ± 17.7	33.8 ± 22.4
Asynch. Ind.$_M$ (ms)	56.8 ± 26.3	36.2 ± 21.4†	45.3 ± 17.4	52.2 ± 31.7
IVD (ms)	41 ± 27	22 ± 27†	46 ± 29	30 ± 30$^{\|}$
EROA (mm^2)	20.8 ± 11.9	14.4 ± 7.6	34.9 ± 21.6	25.3 ± 7.7

Data are presented as the mean value + SD. +dP/dt_{max} = Maximal rate of left ventricular systolic pressure rise; A = peak flow velocity in late diastole; Asynch. Ind. $_{G,B,M}$ = index of global, basal and mid-segmental left ventricular asynchrony; E = peak flow velocity in early diastole; EDV = end-diastolic volume; EF = ejection fraction; EROA = effective regurgitant orifice area; ESV = end-systolic volume; IVD = interventricular delay; JA = jet area; LAA = left atrial area; LV = left ventricular; MAAdef = mitral annulus area deformation; MPI = myocardial performance index; NYHA = New York Heart Association; QoL = Quality of life; Sph. Ind. = sphericity index.

* $P < 0.05$ vs responders baseline.
† $P < 0.05$ vs responders baseline.
‡ $P < 0.01$ vs responders baseline.
** $P < 0.001$ vs responders baseline.
§ $P < 0.0001$ vs responders baseline.
$^{\|}$ $P < 0.05$ vs nonresponders baseline.

restrictive pattern was observed as indicated by a significant reduction of peak A-wave and increase of E/A ratio ($P < 0.05$). No significant changes were found in JA/LAA ratio and in EROA (Table 2).

Considering the overall population, 19 patients (Group A), (18 males, mean age 69 ± 14 years, 11 with IHD and 8 with non-IHD) presented a ≥15% JA/LAA reduction while in 11 patients (Group B) (10 males, mean age 64 ± 9 years, 5 with IHD and 6 with non-IHD) this reduction was not observed. The individual behaviour analysis showed a non-concordant FMR and LVESV reduction (Fig. 3). Among the 19 patients in whom CRT induced a ≥15% JA/LAA reduction, 7 patients were non-responders to LV reverse remodeling while 3 patients, in whom ≥15% JA/LAA was not observed, were responders to LV reverse remodeling. In Group A, the improvement of FMR severity was associated with a significant increase in MAAdef ($P < 0.05$), decrease in Asynch. $Ind._G$ ($P < 0.01$), Asynch. $Ind._B$ ($P < 0.01$), Asynch. $Ind._M$ ($P < 0.05$) and IVD ($P < 0.05$). EF ($P < 0.0001$), MPI ($P < 0.0001$), LV + dP/dt_{max} ($P < 0.01$), were also improved. LVESV and LVEDV were reduced ($P < 0.0001$) although Sph. Ind. was unchanged (Table 3).

In Group B Asynch. $Ind._G$ significantly increased ($P < 0.05$); no significant changes in MAAdef, in Asynch. $Ind._B$, in Asynch. $Ind._M$ and in IVD were observed. LV volumes, EF, MPI, LV + dP/dt_{max} were unchanged.

Regression analysis between all parameters and JA/LAA changes

Multivariate analysis in a stepwise multiple regression model demonstrated that the reduction of Asynch. $Ind._M$ was the variable most strongly related with JA/LAA reduction ($r^2 = 0.697$, $P < 0.01$). Bland and Altman statistic showed a good agreement between the JA/LAA percent change observed and the JA/LAA percent change predicted by the regression formula [42.47 + (Δ Asynch. $Ind._M \times 0.56$)] with all patients but 1 (3.3%) included within the mean ± 2SD (Fig. 2).

Discussion

This is the first report documenting the relationship between the restored ventricular synchrony and the FMR severity reduction in patients treated with CRT. Previous experimental and clinical studies have already demonstrated that the underlying mechanisms of FMR are related to an unbalance of forces that act on mitral valve: ventricular dilation increases the distance between the papillary muscles to the enlarged mitral annulus, restricting leaflet motion and increasing the force needed for effective mitral valve closure. On the other hand, the reduced dP/dt peak decreases the systolic left ventricular-left atrial pressure gradient that acts on the valve leaflets as a closing

Table 3 Effects of CRT in patients who presented FMR improvement (Group A) and in patients in whom FMR did not improve (Group B)

	Group A ($n = 19$)		Group B ($n = 11$)	
	Baseline	Follow-up	Baseline	Follow-up
EF (%)	26 ± 9	36 ± 11[§]	28 ± 6	28 ± 6
LVEDV (ml)	265 ± 85	222 ± 70[§]	275 ± 98	287 ± 124
LVESV (ml)	199 ± 75	148 ± 65[§]	198 ± 74	211 ± 100
MPI	1.1 ± 0.3	0.8 ± 0.3[§]	1.13 ± 0.3	0.9 ± 0.3
LV ± dP/dt_{max} (mmHg/s)	521 ± 194	935 ± 500[‡]	526 ± 363	685 ± 214
Sph. Ind.	0.6 ± 0.1	0.5 ± 0.1	0.6 ± 0.1	0.6 ± 0.1
MAAdef (%)	20 ± 9	25 ± 7[†]	22 ± 10	21 ± 10
Asynch. $Ind._G$ (ms)	50.4 ± 23	34.5 ± 17.3[‡]	42 ± 15	52 ± 24[‖]
Asynch. $Ind._B$ (ms)	39.4 ± 16.6	26.4 ± 15.5[‡]	34 ± 19	42 ± 21
Asynch. $Ind._M$ (ms)	53.8 ± 26.4	35.8 ± 19.9[†]	46.4 ± 14	58.7 ± 34.1
IVD (ms)	46 ± 30	26 ± 30[†]	40 ± 23	26 ± 28

Data are presented as the mean value ± SD. +dP/dt_{max} = Maximal rate of left ventricular systolic pressure rise; Asynch. $Ind._{G,B,M}$ = index of global, basal and mid-segmental left ventricular asynchrony; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; FMR = functional mitral regurgitation; IVD = interventricular delay; LV = left ventricular; MAAdef = mitral annulus area deformation; MPI = myocardial performance index; Sph. Ind. = sphericity index.

[†] $P < 0.05$ vs Group A baseline.

[‡] $P < 0.01$ vs Group A baseline.

[§] $P < 0.0001$ vs Group A baseline.

[‖] $P < 0.05$ vs Group B baseline.

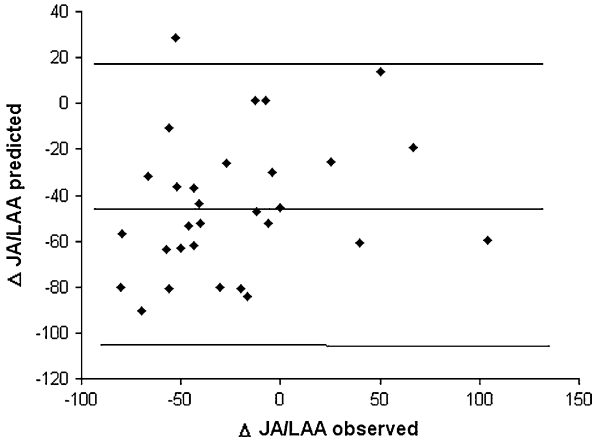

Figure 2 Bland and Altman statistic showing the agreement between the JA/LAA percent changes observed and JA/LAA percent changes predicted. JA = jet area; LAA = left atrial area.

force.[12–14] The loss of mitral annulus contraction is another factor that has been demonstrated to influence mitral valve regurgitation.[23] Mitral annulus is a vital component of the mitral valve/left atrial/left ventricular complex which contributes to a timely, efficient and competent valve closure as well as an unimpeded LV filling during diastole. Mitral annulus expansion and motion facilitates filling in diastole, while annular size reduction aids leaflet coaptation and normal closure in early systole.[24] This sphincteric action of the annulus can be affected by haemodynamic conditions, such end-stage of HF.[25] In our FMR reduction responders, the improvement of the mitral regurgitation severity was associated with a significant improvement of LV systolic function parameters (EF, MPI, dP/dt) as well as with a more effective annulus contraction and with a reverse ventricular remodeling as indicated by LVEDV and LVESV reduction. Thus in 19 of 30 patients studied, CRT corrected the imbalance between the forces acting on mitral valve and enhanced the sphincteric action of the annulus.

The aim of our study was to evaluate if a more synchronous ventricular contraction plays a role in mitral valve regurgitation improvement.

The relationship between ventricular asynchrony and mitral regurgitation has been already demonstrated: Xiao et al. in 1991 showed that the left bundle branch block (LBBB) prolonging pre-ejection and relaxation time lengthened the duration of mitral regurgitation.[26] More recently Erlebacher et al. reported that in patients with dilated cardiomyopathy FMR is strongly correlated with prolonged QRS duration in general, and with LBBB and right ventricular pacing in particular, whereas other conduction abnormalities were not associated with FMR.[27] The same authors in a group of 1270 patients showed a higher prevalence of moderate to severe mitral regurgitation in patients with QRS duration $>$ 130 ms compared with patients with QRS duration $<$ 130 ms.

In this study, by using TDI, we evaluated basal-segmental, mid-segmental and global LV asynchrony. Interestingly in responders to FMR improvement, CRT induced a resynchronization of global, basal and mid-LV segments. LV basal resynchronization might be likely responsible for the improved annular sphincteric function, however, the stepwise multivariate linear regression analysis showed that among the percent changes of all parameters evaluated, the mid-LV segments asynchrony reduction is the most significant factor for JA/LAA reduction.

It is likely that a more synchronous contraction of the papillary muscles, inserted in the LV mid-segments, plays an important role in FMR improvement in this group of patients, nevertheless LV reverse remodeling and enhanced contractile efficiency give an important contribute. Moreover another interesting finding was the observed different individual behaviour in FMR severity and LVESV change (Fig. 3). The latter is generally considered a criterion of LV remodeling reversal induced by CRT. In our study CRT caused a significant reduction of FMR regardless of LV reverse remodeling. In fact 7 patients in whom FMR reduction was achieved were nonresponder to LVESV reduction while in 3 patients LVESV reduction occurred without FMR improvement. The analysis of LV synchronicity parameters showed a strong correlation between ventricular resynchronization and FMR improvement. In patients who presented FMR reduction, basal, mid- and global LV asynchrony was improved while the latter was worsened in those patients in whom FMR severity was not improved.

It is well established that FMR is a multifactorial complication of HF where ventricular remodeling, decreased contractility, loss of mitral annular function represent important underlying mechanisms; our data reveal that ventricular asynchrony is another factor influencing the severity of FMR. Correction of FMR is a major issue in the management of patients with severe HF since it has been shown to be a critical determinant of their poor prognosis. To date pharmacological therapies principally with ACE-inhibitors employment, have been demonstrated to reduce FMR by affecting ventricular remodeling and contractility, as well as some surgical techniques, aimed at correcting the adverse effects of ventricular remodeling are

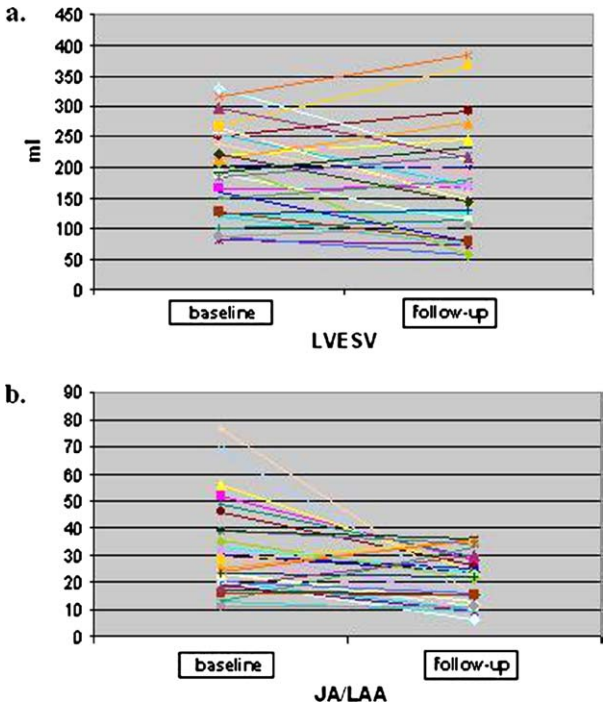

Figure 3 Individual behaviour of LVESV (a) and FMR severity change (b) after 6 months of cardiac resynchronization therapy. FMR = functional mitral regurgitation; LVESV = left ventricular end-systolic volume; JA = jet area; LAA = left atrial area.

developing. We have shown that CRT is able to improve FMR by correcting all the underlying mechanisms (that is reduced contractility, ventricular remodeling, loss of annular function and ventricular asynchrony). These multiple effects of CRT further support its employment in patients with HF and FMR.

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