Reduced mitral regurgitation in heart failure patients submitted to cardiac resynchronization therapy: a short-term prospective study

Francesco Zanon, Silvio Aggio, Enrico Baracca, Claudio Bilato, Giorgio Corbucci*, Gianluca Rigatelli, Pietro Zonzin

*Division of Cardiology, General Hospital, Rovigo, *Vitatron Medical Italia, Bologna, Italy*

Key words:
Cardiac resynchronization therapy; Heart failure; Mitral regurgitation.

Background. **The intraventricular delay is a determinant of functional mitral regurgitation (MR). MR contributes to the progression of congestive heart failure (CHF) and represents a marker of a worse outcome. The aim of this study was to test the hypothesis that cardiac resynchronization therapy (CRT) significantly reduces MR in CHF patients with ventricular conduction defects.**

Methods. **We studied 45 consecutive patients (37 males, 8 females, mean age 72 ± 9 years) in NYHA class III-IV, with left ventricular ejection fraction < 35%, QRS duration > 150 ms with left bundle branch block or already paced in the right ventricle, and MR score ≥ 1. We compared the QRS duration and the basal peak of the V-wave before and 15 min after CRT. Before implantation and 1 week after we measured ejection fraction, systolic mitral annulus diameter, MR area, left atrial area, MR area expressed as the percentage of the left atrial area (%MR area), and MR score (range 1-4).**

Results. **The QRS duration before and after CRT was 195 ± 30 and 156 ± 17 ms ($p < 0.01$) respectively. Significant decreases were observed in the systolic mitral annulus diameter (-7.9%, $p < 0.001$), MR area (-38%, $p < 0.001$), MR score (-33.4%, $p < 0.001$), left atrial area (-5.9%, $p < 0.05$), and %MR area (-36.2%, $p < 0.001$). The peak of the V-wave decreased by 33%. The ejection fraction increased by 46% ($p < 0.001$).**

Conclusions. **CRT significantly reduces MR and improves cardiac function in patients with CHF and ventricular conduction defects. The combination of the degree of MR and a low ejection fraction and large QRS duration may contribute to a more reliable patient selection for CRT.**

(Ital Heart J 2004; 5 (11): 826-830)

Received May 4, 2004; revision received July 29, 2004; accepted September 14, 2004.

Address:

Dr. Francesco Zanon

Divisione di Cardiologia
Ospedale Civile
Via Tre Martiri, 140
45100 Rovigo
E-mail:
franc.zanon@iol.it

Introduction

Dilated cardiomyopathy, characterized by enlargement of the cardiac chambers and depressed ventricular function, is a common cause of congestive heart failure (CHF) and is associated with a high mortality. Ventricular conduction defects, as evidenced by a QRS duration > 130 ms and/or left bundle branch block (LBBB), are common in the advanced heart failure population. The additional presence of mitral regurgitation (MR) contributes to the progression of ventricular dysfunction and represents a marker of a worse outcome. The mechanisms behind the development of MR in cardiomyopathy are complex. The degree of MR may be influenced not only by dilation of the mitral annulus but also by the geometry and function of the papillary muscles, chordae tendineae and mitral leaflets themselves[1,2].

Cardiac resynchronization therapy (CRT) has recently been proposed as a new approach for the management of CHF associated with ventricular conduction defects: acute studies have shown a marked hemodynamic improvement during left ventricular or biventricular pacing in this patient population.

The data from acute and mid-term follow-ups indicate that CRT improves hemodynamics, exercise duration, functional class, and quality of life[3-5].

The mechanisms by which CRT may improve symptoms in CHF include normalization of ventricular wall motion, optimization of atrioventricular filling, and reduction of MR. MR in patients with left ventricular dysfunction and conduction delay with a QRS interval > 130 ms may modify the long-term prognosis[6]. The intraventricular delay is a determinant of functional MR, and we tested the hypothesis that CRT significantly reduces it through the resynchronization of myocardial contraction.

Methods

Protocol. The inclusion criteria were NYHA class III-IV despite optimal medical treatment, a severely impaired left ventricular function with ejection fraction < 35%, QRS duration > 150 ms associated with LBBB or a previously implanted pacemaker with right ventricular apex stimulation, and an MR score (range 1-4) ≥ 1[7]. The exclusion criteria were structural mitral valve disease and any concomitant disease implying a life expectancy < 6 months.

The study was approved by the local Ethics Committee and informed consent for participation in the investigation was obtained from each patient prior to enrolment.

Patient population. Forty-five consecutive patients (37 males, 8 females, mean age 72 ± 9 years) were enrolled; 9 patients had a previously implanted pacemaker with right ventricular apex stimulation; 5 patients were in chronic atrial fibrillation with bradycardia and then paced in the biventricular VVIR mode. All other patients were paced in the DDD biventricular mode.

Pacemaker implantation and programming. Biventricular stimulation was performed simultaneously in both ventricles. The left ventricular lead was placed in a tributary vein of the coronary sinus, in a lateral or postero-lateral position. In 43 out of 45 patients an over-the-wire catheter was used. The right ventricular lead was placed in the apex of the right ventricle in accordance with the standard procedure. A bipolar atrial lead was placed in the right atrial appendage in patients with sinus rhythm and the programmed mode was DDD with the atrioventricular interval set at 130 ms to guarantee constant ventricular capture. No additional procedure for the optimization of the atrioventricular delay was performed. The mean time of the procedure was 126 min, of which 24 min for left ventricular lead positioning and 34 min for fluoroscopy.

Echo measurements. Before implantation, all subjects underwent a baseline echocardiographic examination in order to assess left ventricular ejection fraction (Simpson method[8], two-dimensional), systolic mitral annulus diameter (SMAD), MR area, left atrial (LA) area, MR area expressed as the percentage of the LA area (%MR area), and the MR score which ranged from 1 to 4 and was assessed through the maximum color Doppler area of the regurgitant jet referred to the LA area. Patients with grade 0 were classified as having no MR, grade 1 = mild MR, grade 2 = moderate MR, grade 3 = moderate to severe, and grade 4 = severe MR[7]. The MR volume was quantified by calculating the difference between the aortic outflow volume and the mitral inflow volume as assessed at pulsed-wave Doppler[9]. The left ventricular end-systolic volume was quantified using the Simpson method[8]. Echocardiographic evaluation was performed by means of a commercially available imaging system (General Electric VIVID Five, GE Medical System, Milwaukee, WI, USA) equipped with a 2.5-3.6 MHz transducer. Echo recordings were obtained through the apical 4-chamber view with the patient lying down in the left lateral position. All measurements were taken for five consecutive cycles and the mean values were calculated.

Invasive hemodynamic measurements. During the implantation procedure the peak of the V-wave was invasively measured using a Swan-Ganz catheter during right ventricular pacing in patients with a previously implanted pacemaker, and in spontaneous rhythm in the remaining patient population. These data, representing the hemodynamic baseline, were compared with the corresponding values measured after 15 min of CRT.

QRS duration. The baseline QRS duration was measured at enrolment during right ventricular pacing in patients with a previously implanted pacemaker and in spontaneous rhythm in the remaining patient population. The QRS duration corresponding to CRT was measured during the implantation procedure.

Follow-up. One week after implantation all patients underwent a new echocardiographic examination to compare the pre- and post-implant data. After 1 week, we were able to assess patients with no risks of lead displacement before any left ventricular remodeling occurs.

Statistical analysis. All data are reported as mean ± SD. The variables were analyzed using the two-tailed paired Student's t-test. A p value ≤ 0.05 was considered as statistically significant. The correlation coefficient of the linear regression analysis was assessed using the Pearson test.

Results

Table I summarizes the echocardiographic, hemodynamic and ECG data comparing the baseline values with those obtained following CRT. The QRS duration was 195 ± 30 ms at baseline and significantly decreased with CRT to 156 ± 17 ms ($p < 0.01$), with a 21% reduction. The programmed atrioventricular delay (130 ms) allowed a constant and reliable biventricular capture in all patients in sinus rhythm.

Statistically significant variations were observed in all echocardiographic parameters. SMAD (-7.9%, $p < 0.001$), MR area (-38%, $p < 0.001$), and the MR score (-33.4%, $p < 0.001$) were all significantly decreased. The %MR area was also found to be significantly reduced (-36.2%, $p < 0.001$). Figure 1 shows, for each patient, the degree of %MR area reduction with CRT as a function of its basal value: the higher the %MR area, the greater its reduction.

Table I. Echocardiographic, hemodynamic and ECG data at baseline and after cardiac resynchronization therapy (CRT).

	Baseline	Post-CRT	p
EF (%)	23.74 ± 5.63	34.67 ± 7.30	< 0.001
SMAD (mm)	38.62 ± 3.78	35.55 ± 3.97	< 0.001
LA area (cm^2)	30.71 ± 10.78	28.90 ± 10.00	< 0.05
MR area (cm^2)	6.81 ± 4.83	4.22 ± 3.62	< 0.001
%MR area (%)	22.80 ± 13.11	14.53 ± 11.77	< 0.001
MR score (1-4)	2.06 ± 0.83	1.42 ± 0.61	< 0.001
V-wave (mmHg)	26 ± 11	17.4 ± 9.7	< 0.05
QRS (ms)	195 ± 30	156 ± 17	< 0.01
MRV (ml)	135 ± 79	83 ± 54	< 0.0004
LVESV	266 ± 77	217 ± 83	< 0.0001

EF = ejection fraction; LA = left atrial; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; MRV = mitral regurgitation volume; SMAD = systolic mitral annulus diameter. %MR area = mitral regurgitation area expressed as the percentage of the LA area.

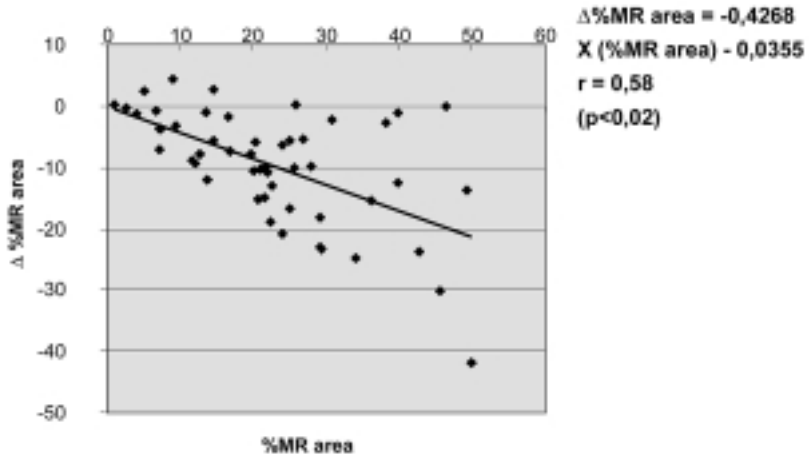

Figure 1. *The mitral regurgitation area expressed as the percentage of the left atrial area (%MR area) significantly decreased with cardiac resynchronization therapy as compared to the basal value. The correlation coefficient of the linear regression analysis was assessed using the Pearson test (r = 0.58).*

The LA area (-5.9%, $p < 0.05$), MR volume (-38%, $p < 0.0004$) and left ventricular end-systolic volume (-18%, $p < 0.0001$) were all significantly decreased. On the other hand, the ejection fraction increased by a mean of 46% following CRT with respect to the baseline value ($p < 0.001$). The invasively assessed peak of the V-wave during implantation was significantly reduced by 33% with CRT compared to baseline. Figure 2 shows an example of the traces used to assess the V-wave during CRT, right ventricular pacing, and no pacing. This dramatic improvement, with a reduction > 50% in the V-wave value, was observed in 18 patients (40%).

Discussion

Mitral valve regurgitation may remarkably contribute to the development of symptoms and may influence the clinical prognosis of patients with dilated cardiomyopathy. The degree of MR may increase due to dilation of the annulus and to the marked tethering forces acting on the mitral leaflets[8]. The mechanically abnormal left ventricular contraction in the presence of an intraventricular delay may so dramatically alter the position of the valve leaflets during systole as to induce or at least increase regurgitation[10]. It has been demonstrated that the asynchronous activation of the medial and lateral segments supporting the papillary muscles may independently contribute to functional MR in CHF patients[11,12].

Our study shows that CRT improves, on average, all echocardiographic, hemodynamic and ECG parameters in this patient population, and mainly the MR area. The improvements in the hemodynamic, ECG and echocardiographic parameters were similar in patients with and without atrial fibrillation, and no significant differences were seen between the two groups. However, we cannot extrapolate this observation to the general patient population with coexisting CHF and atrial

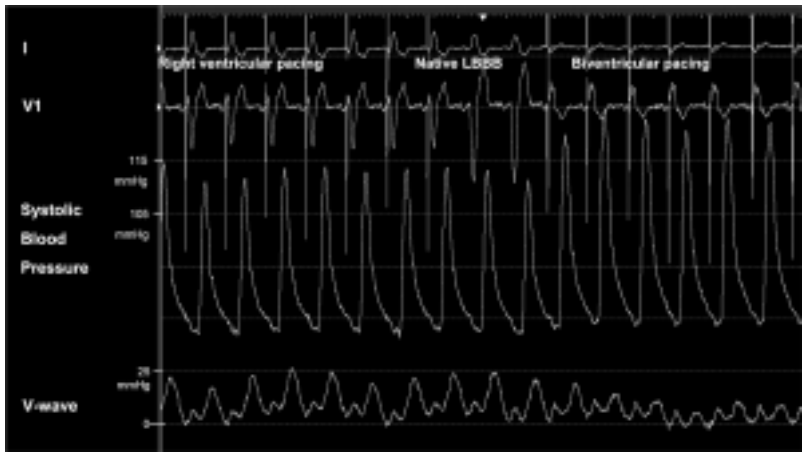

Figure 2. *Assessment of the V-wave in patient no. 6 during right ventricular stimulation, two spontaneous beats and cardiac resynchronization therapy. LBBB = left bundle branch block.*

fibrillation due to the relative small number of patients with atrial fibrillation in this study.

Our data are in accordance with those published by Breithardt et al.[13] relative to the acute effects of CRT on functional MR in a similar patient population. CRT acutely reduces the severity of MR in heart failure patients with LBBB independently of the potential long-term reverse remodeling of the left ventricular shape and size[14]. Breithardt et al. demonstrated that the immediate 40% decrease in the MR area with CRT is quantitatively related to an increased left ventricular dP/dt max and to an increased transmitral pressure gradient.

In dilated CHF patients with LBBB, the abnormal mechanics of contraction due to an abnormal intraventricular delay alters the balance between the tethering and closing forces, impeding an effective mitral valve closure. The 1-week positive effect of CRT on functional MR supports the hypothesis that the individual degree of ventricular asynchrony may alter the leaflet tethering forces and aggravate regurgitation, independently of the left ventricular geometry.

The evident and important benefit of CRT is probably also related to the selected population, and mainly to the relatively low ejection fraction and relatively long QRS duration at enrolment. Of course, the correlation between the short-term results of CRT and the long-term clinical outcome needs to be further confirmed by future studies.

Study limitations. We did not investigate the underlying mechanisms of the beneficial effects of pacing on hemodynamic parameters such as left ventricular dP/dt. We optimized the left ventricular pacing site only of the lateral or postero-lateral position, excluding the anterior or septal ventricular segment. The atrioventricular delay was set at 130 ms only to guarantee a complete capture of the ventricles, and the V-V interval was not optimized because the study started when it was not possible to adjust this parameter in every device. Optimization of the V-V interval could have introduced a new confounding factor. On the other hand, we started from the assumption that optimizing these variables would only confirm or improve the obtained positive results. On the basis of our data it is not possible to evaluate the impact of the improvement in MR alone on the global benefit provided by CRT. Therefore the parameters that showed the most important variations were all those related to MR together with the ejection fraction and V-wave. The degrees of inter- and intraventricular dyssynchrony before and after implantation were not evaluated. Hence, it was not possible to correlate the degree of dyssynchrony with the degree of MR with and without CRT.

In conclusion, this short-term study demonstrated that CRT *per se* significantly improves cardiac function in patients with CHF, a large QRS and MR. The combination of the degree of MR, a low ejection fraction and a large QRS duration may contribute to a more reliable patient selection for CRT. The clinical impact of CRT in patients with MR needs to be evaluated in long-term follow-up studies.

Acknowledgments

Graziano Boaretto, Paola Raffagnato and Antonella Tiribello helped with implantation and data collection. Giovanna Zucchi provided secretarial support. We would like to acknowledge their contributions.

References

1. Rosario LB, Stevenson LW, Solomon SD, Lee RT, Reimond SC. The mechanism of decrease in dynamic mitral regurgitation during heart failure treatment: importance of reduc-

tion in the regurgitant orifice size. J Am Coll Cardiol 1998; 32: 1819-24.
2. Gras D, Leclercq C, Tang AS, Bucknall C, Luttikhuis HO, Kirstein-Pedersen A. Cardiac resynchronization therapy in advanced heart failure: the multicenter InSync clinical study. Eur J Heart Fail 2002; 4: 311-20.
3. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001; 344: 873-80.
4. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002; 346: 1845-53.
5. Varma C, Camm AJ. Pacing for heart failure. Lancet 2001; 357: 1277-83.
6. Etienne Y, Mansourati J, Touiza A, et al. Evaluation of left ventricular function and mitral regurgitation during left ventricular-based pacing in patients with heart failure. Eur J Heart Fail 2001; 3: 441-7.
7. Chirillo F, Totis O, Salvador L, et al. Valvulopatia mitralica. In: Santini M, ed. Trattato di cardiologia. Vol II. Milano: Excerpta Medica, 2000: 1711-55.
8. 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: 358-67.
9. Enriquez-Sarano M, Bailey KR, Seward JB, et al. Quantitative Doppler assessment of valvular regurgitation. Circulation 1993; 87: 841-8.
10. Erlebacher JA, Barbarash S. intraventricular conduction delay and functional mitral regurgitation. Am J Cardiol 2001; 88: 83-6.
11. Nelson GS, Curry CW, Wyman BT, et al. Predictors of systolic augmentation from left ventricular preexcitation in patients with dilated cardiomyopathy and intraventricular conduction delay. Circulation 2000; 101: 2703-9.
12. Messas E, Guerrero JL, Handschumacher MD, et al. Paradoxic decrease in ischemic mitral regurgitation with papillary muscle dysfunction: insights from three-dimensional and contrast echocardiography with strain rate measurement. Circulation 2001; 104: 1952-7.
13. Breithardt OA, Sinha AM, Schwammental E, et al. Acute effects of cardiac resynchronization therapy on functional mitral regurgitation in advanced systolic heart failure. J Am Coll Cardiol 2003; 41: 765-70.
14. Saxon LA, De Marco T, Schafer J, Chatterjee K, Kumar UN, Foster E. Effects of long-term biventricular stimulation for resynchronization on echocardiographic measures of remodeling. Circulation 2002; 105: 1304-10.