Acute Effects of Initiation and Withdrawal of Cardiac Resynchronization Therapy on Papillary Muscle Dyssynchrony and Mitral Regurgitation

Claudia Ypenburg, MD,* Patrizio Lancellotti, MD, PhD,† Laurens F. Tops, MD,* Gabe B. Bleeker, MD,* Eduard R. Holman, MD, PhD,*† Luc A. Piérard, MD, PhD,† Martin J. Schalij, MD, PhD,† Jeroen J. Bax, MD, PhD*

Leiden, the Netherlands; and Liege, Belgium

Objectives The purpose of this study was to evaluate the relationship between dyssynchrony involving the mitral valve apparatus and the acute improvement in mitral regurgitation (MR) after cardiac resynchronization therapy (CRT). The effect of interruption of CRT at 6 months’ follow-up on dyssynchrony and MR was also evaluated.

Background Mitral regurgitation may improve acutely after CRT, but the precise mechanism is not fully understood.

Methods Out of 63 consecutive patients with baseline MR, 25 patients showed an acute reduction in MR severity immediately after CRT. This selected group of 25 patients (age 68 ± 10 years, left ventricular ejection fraction 23 ± 8%) was evaluated in the current study. Echocardiography including speckle tracking strain analysis was performed at baseline, after CRT initiation, and during interruption of CRT at 6 months’ follow-up to study the relationship between dyssynchrony between the papillary muscles and severity of MR.

Results According to the inclusion criteria, all patients showed an immediate improvement in MR after CRT (vena contracta width decreased from 0.54 ± 0.15 cm to 0.39 ± 0.13 cm; p < 0.001), accompanied by an improvement in mitral deformation indexes. Furthermore, dyssynchrony between the papillary muscles decreased from 169 ± 69 ms to 25 ± 26 ms (p < 0.001). Importantly, these beneficial effects were maintained at 6 months’ follow-up, but acute loss of resynchronization (from 26 ± 28 ms to 134 ± 51 ms; p < 0.001) was observed after interruption of CRT, with an acute recurrence of MR and worsening in mitral deformation indexes.

Conclusions Cardiac resynchronization therapy can acutely reduce MR in patients with dyssynchrony involving the papillary muscles; interruption of CRT at 6 months’ follow-up, however, resulted in acute loss of resynchronization with recurrence of MR. (J Am Coll Cardiol 2007;50:2071–7) © 2007 by the American College of Cardiology Foundation

Recent studies have demonstrated that cardiac resynchronization therapy (CRT) may acutely improve functional mitral regurgitation (MR) (1–3). However, the exact mechanism underlying the reduction in MR after CRT remains unclear. Preliminary results suggest that the acute improvement in MR may be related to improved coordination of papillary muscle contraction (2).

In this context, we hypothesized that patients with dyssynchrony between the anterior and posterior papillary muscles (APM-PPM dyssynchrony) will exhibit an acute reduction in MR after CRT, owing to resynchronized papillary muscle contraction. Furthermore, it was hypothesized that deactivating CRT after 6 months would cause loss of resynchronization and acute recurrence of MR.

Accordingly, the study population consisted of selected patients with moderate to severe MR who showed an immediate reduction in MR after CRT initiation. Extensive echocardiographic evaluations were performed, including speckle tracking radial strain analysis, to assess APM-PM dyssynchrony. Patients were evaluated before and immediately after CRT and again evaluated after 6 months with CRT on and off.

Methods

Patients and study protocol. Between January 2005 and July 2006, 186 patients received a CRT device according to the current guidelines: New York Heart Association (NYHA) functional class III or IV, depressed left ventricular (LV) function, and QRS duration >120 ms.

From the *Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands; and the †Department of Cardiology, University Hospital Sart Tilman, Liege, Belgium. Supported by the Dutch Heart Foundation, grant no. 2002B109. John Gorscan III, MD, FACC, served as Guest Editor for this article.

Manuscript received April 20, 2007; revised manuscript received August 14, 2007, accepted August 20, 2007.
function (ejection fraction <35%), and wide QRS complex (≥120 ms) (4). Sixty-three of these patients had significant MR at baseline, with 25 patients showing an acute improvement in MR severity acutely after CRT initiation. These 25 patients formed the focus of the current study.

The study protocol included echocardiography at baseline, the day after implantation, and at 6 months’ follow-up. After data acquisition at 6 months’ follow-up, CRT was interrupted to perform echocardiography during intrinsic conduction or in right ventricular pacing in patients without intrinsic conduction. Furthermore, assessment of clinical status was performed at baseline and after 6 months of CRT.

Echocardiography. All patients underwent standard transthoracic 2-dimensional (2D) echocardiography, including quantification of MR, LV function, global and local LV remodeling, assessment of mitral valve deformation indexes, and speckle tracking strain analysis to assess APM-PPM dysynchrony. All echocardiographic studies were performed the day before implantation, the day after implantation, and at 6 months’ follow-up with CRT on and off. The CRT device was turned off for 5 min before the acquisition started. Patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed Vivid 7, General Electric-Vingmed, Milwaukee, Wisconsin). 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). Standard 2D and color Doppler data, triggered to the QRS complex, were saved in cine-loop format. For each measurement, ≥3 cardiac cycles were averaged. Investigators were not blinded for the pacemaker settings.

Quantification of MR and mitral deformation indexes. The severity of MR was measured from the apical 4-chamber view, by measuring the width of the vena contracta (5). Left atrial (LA) area and regurgitant jet area were measured by planimetry from the apical 4-chamber view, allowing calculation of the ratio of regurgitant jet area to LA area (6). The severity of MR was graded as mild (vena contracta width <0.3 cm, LA area <4 cm², or jet area/LA area <20%), moderate (vena contracta width 0.3 cm to 0.7 cm, jet area/LA area 20% to 40%) or severe (vena contracta width >0.7 cm, jet area/LA area >40%) as recommended by the American College of Cardiology/American Heart Association 2006 guidelines (6,7).

The maximal rate of LV systolic pressure increase (dP/dt) was estimated from the steepest rising segment on the continuous-wave Doppler regurgitant signal (8). 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) toward the LV apex was measured by the distance between leaflet coaptation and the mitral annulus plane in the apical 4-chamber view. Mitral annulus diameter was measured at end-systole and -diastole in the 4-chamber view. Annular contraction was calculated as: (end-diastolic diameter – end-systolic diameter)/end-diastolic diameter (9).

Global and local LV remodeling. The LV volumes (end-diastolic and end-systolic) and ejection fraction were calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson technique (10). The distance between the posterior papillary muscle head and the intervalvular fibrosa (PPM-fibrosa) in the long-axis view measured the apical displacement of the PPM (9).

Speckle tracking strain analysis. Radial strain was assessed on LV short-axis images at the papillary muscle level, using speckle tracking analysis (11–13). Time-strain curves for all of the 6 LV segments (septal, anteroseptal, anterior, posterior, lateral, and inferior) were constructed. The segments adjacent to the papillary muscles were noted (Fig. 1). Peak radial strain and time from QRS onset to peak radial strain for the LV segments were obtained, and the severity of APM-PPM dysynchrony could be determined (Fig. 2). Radial strain measurements were reproducible and showed minimal variability (interobserver correlation coefficient r = 0.94; intraobserver correlation coefficient r = 0.96).

CRT implantation. A coronary sinus venogram was obtained using balloon catheter, followed by the insertion of the LV pacing lead. An 8-F guiding catheter was used to position the LV lead (Easytrak 4512-80, Guidant Corp., St. Paul, Minnesota, or Attain-SD 4189, Medtronic, Minneapolis, Minnesota) in the coronary sinus. The preferred position was a lateral or posterolateral vein (14). 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 Corp., or Insync III or Insync Sentry, Medtronic).

Clinical evaluation at 6 months’ follow-up. Clinical evaluation was performed before implantation and after 6 months of CRT. The NYHA functional class was used to evaluate heart failure symptoms and scored by an independent physician who was blinded to all other patient data. Quality-of-life score was assessed using the Minnesota Living with Heart Failure Questionnaire (15). Exercise tolerance was assessed using the 6-min walk test (16). In all of the patients, QRS duration was measured from the surface ECG using the widest QRS complex from the leads II, V₁, and V₆, at baseline and after implantation.
Statistical analysis. Continuous variables are expressed as mean ± SD. Categoric data are summarized as frequencies and percentages.

Clinical parameters were assessed at baseline and at 6 months’ follow-up. Comparison of these data during follow-up was performed with the paired student \( t \) test (continuous variables) and the McNemar test (NYHA functional class, MR severity). A \( p \) value of 0.05 was considered to be statistically significant.

All of the echocardiographic studies were performed the day before implantation, the day after implantation, and at 6 months’ follow-up with CRT on and off. Comparison of these data during follow-up was performed by applying the statistical tests mentioned. Baseline parameters were compared with parameters immediately after implant, parameters immediately after implant with 6-month follow-up data, and 6-month follow-up data with the interruption parameters. Therefore, to adjust for inflation of the type I error with multiple tests, we applied a Bonferroni correction and considered a \( p \) value of <0.017 (0.05/3) to be statistically significant.

Results

Patients. Baseline characteristics of the 25 patients (16 men, age 68 ± 10 years) are summarized in Table 1. A total of 19 patients (76%) had moderate MR, and 6 patients (14%) had severe MR before CRT implantation. Speckle tracking radial strain analysis showed that dyssynchrony between the anterior and posterior papillary muscle was present in all patients (169 ± 69 ms, range 92 to 254 ms). In 18 patients (72%), the APM was located adjacent to the lateral LV segment, and adjacent to the anterior LV segment in 7 patients (28%); the posterior papillary muscle (PPM) was located adjacent to the inferior LV segment in 22 patients (88%) and adjacent to the posterior LV segment in 3 patients (12%).

Device implantation was successful in all patients, and no procedure-related complications were observed. One patient...
died of worsening heart failure before the 6-month follow-up evaluation.

**Changes in MR, mitral deformation indexes, and LV function.** According to the inclusion criteria, all patients showed an immediate reduction in severity of MR after CRT; vena contracta width decreased from 0.54 ± 0.15 cm to 0.39 ± 0.13 cm (p < 0.001). Importantly, this reduction in MR was maintained at 6 months' follow-up (vena contracta width 0.37 ± 0.11 cm; p = NS vs. immediately after CRT), followed by an immediate increase of MR when the pacemaker was turned off at 6 months (Table 2, Fig. 3).

The acute improvement in MR after CRT implantation was accompanied by an immediate improvement in LV dP/dt, a reduction in LV end-systolic volume, and a deterioration of LV function. The LV end-diastolic volume did not change acutely. At 6 months' follow-up, the improvement in LV volumes and LV function was even more pronounced, with evidence of significant LV reverse remodeling. An acute deterioration of these parameters, except for LV end-diastolic volume, occurred during interruption of CRT at 6 months' follow-up.

Furthermore, acute local remodeling after initiation of CRT was noted, as demonstrated by an acute reduction in PPM-fibrosa distance from 6.7 ± 0.14 cm to 6.4 ± 0.12 cm (p < 0.001), with a further reduction to 6.1 ± 0.6 cm at 6 months' follow-up (p = 0.004 vs. after CRT initiation).

Finally, acute reduction in MR was accompanied by an acute improvement in mitral deformation indexes. An acute improvement in tenting area was observed (from 7.8 ± 1.0 cm² to 7.2 ± 1.0 cm²; p < 0.001), with reduction in coaptation height (from 1.94 ± 0.18 cm to 1.79 ± 0.14 cm; p < 0.001) and improvement in mitral annular coaptation (from 16 ± 4% to 20 ± 4%; p < 0.001). This improvement was maintained or even further improved after 6 months of CRT, followed by an acute deterioration of these parameters after interruption of CRT.

**Changes in dyssynchrony between the papillary muscles.** Speckle tracking analysis was possible in all patients; however, 31 of the 588 evaluated segments (5%) had to be eliminated because of negative strain values. In case of very low but positive strain values the segment was included when appearing hypokinetic or dyskinetic on the short-axis views.
Initiation of CRT exhibited resynchronization of the papillary muscles as demonstrated by a decrease in APM-PPM dyssynchrony from 169 ± 69 ms to 25 ± 26 ms (p < 0.001) (Fig. 4). This reduction in dyssynchrony was maintained at 6 months' follow-up (25 ± 26 ms immediately after CRT vs. 26 ± 28 ms at 6 months' follow-up; p = NS). However, during interruption of CRT, APM-PPM dyssynchrony increased acutely to 134 ± 51 ms (Fig. 5).

Clinical evaluation at 6 months' follow-up. After 6 months of CRT, 18 patients improved 1 NYHA functional class and 3 patients improved 2 NYHA functional classes (p < 0.001). The quality-of-life score decreased from 35 ± 17 to 19 ± 14 (p < 0.001). In addition, a significant increase in 6-min walking distance was noted (from 296 ± 101 m to 395 ± 95 m; p < 0.001).

Patients without reduction of MR after CRT. Of note, analysis of the 38 patients who did not show an immediate reduction in MR severity after CRT revealed that these patients had minimal APM-PPM dyssynchrony at baseline compared with the patients who did show an immediate reduction after CRT initiation (38 ± 55 ms vs. 169 ± 69 ms; p < 0.001).

Discussion

The results of the present study illustrate that the mechanism underlying acute improvement in MR after CRT may be attributable to resynchronized contraction of the papillary muscles. Interruption of CRT at 6 months' follow-up resulted in acute loss of APM-PPM resynchronization with an acute deterioration of MR. Furthermore, the acute improvement in MR was accompanied by an improvement in mitral deformation indexes, whereas CRT interruption at 6 months' follow-up was associated with an acute deterioration of these parameters.

CRT and reduction in MR. As demonstrated in various randomized trials, CRT in patients with moderate-to-severe heart failure results in a sustained improvement in symptoms and LV systolic function and reverse remodeling (17–21). Furthermore, CRT may also reduce MR (19,21–24). For instance, the MIRACLE (Multicenter InSync Randomized Clinical Evaluation) trial reported a significant reduction in MR in the CRT group after 6 months (MR jet area decreased from 7.31 ± 6.14 cm² to 4.81 cm²; p < 0.01) (21). This reduction in MR has been attributed to LV reverse remodeling, with a secondary reduction in mitral annular diameter and as a consequence restored mitral valve closure, which is a long-term effect of CRT.

However, other studies reported an immediate improvement in MR severity after CRT initiation. Breithardt et al. (1) studied 24 heart failure patients (LV ejection fraction 21 ± 6%) and demonstrated that the severity of MR improved immediately after CRT, with a reduction in effective regurgitant orifice area from 25 ± 19 mm² to 13 ± 8 mm² (p < 0.01). A similar acute reduction in MR severity was demonstrated by Kanzaki et al. (2); the regurgitant volume decreased from 40 ± 20 ml to 24 ± 17 ml (p < 0.01) (2). In line with these results, the present study showed an immediate reduction in MR severity after CRT in all patients (vena contracta width from 0.54 ± 0.15 cm to 0.39 ± 0.13 cm; p < 0.001). This improvement was
accompanied by a significant decrease in LV end-systolic volume and an increase in LV dP/dt and LV function similar to those of the earlier studies (1,2). Furthermore, as shown in Table 2, mitral deformation indexes and local LV remodeling showed an acute improvement after CRT.

**Relation between MR and dyssynchrony.** Preliminary results suggested that the immediate reduction in MR may be caused by resynchronization of the papillary muscles (2). Furthermore, increased closing force of the mitral leaflets may also be important for the improvement in MR (1). The present findings further support this hypothesis.

First, LV dP/dt almost doubled after CRT initiation (702 ± 344 mm Hg to 1,153 ± 620 mm Hg; p < 0.001), with an improvement in LV ejection fraction (from 23 ± 8% to 28 ± 9%, p < 0.001), which effectively counteracts the increased tethering forces (with a decrease in tenting area from 7.8 ± 1.0 mm² to 7.2 ± 1.0 mm²; p < 0.001). Breithardt et al. (1) showed a somewhat similar increase in LV dP/dt acutely after CRT.

Furthermore, all 25 included patients showed an immediate reduction in APM-PPM dyssynchrony (from 169 ± 69 ms to 25 ± 26 ms; p < 0.001) accompanied by a reduction in MR severity. A similar reduction in time delay between the papillary muscles after CRT initiation was demonstrated by Kanzaki et al. (2) (106 ± 74 ms to 39 ± 43 ms; p < 0.001), who evaluated 26 heart failure patients (LV ejection fraction 24 ± 6%, 73% ischemic cardiomyopathy) with at least mild MR before and after CRT using mechanical activation strain maps.

Importantly, assuming that the improvement in MR is biventricular pacing dependent, it could be anticipated that interruption of biventricular pacing would lead to an immediate desynchronization of the papillary muscles with acute deterioration of MR. Indeed, all acute improvements in echocardiographic parameters were maintained or more improved during follow-up; in particular, MR severity (vena contracta width 0.39 ± 0.13 cm after CRT to 0.37 ± 0.11 cm after 6 months; p = NS) and dyssynchrony between the papillary muscles (25 ± 26 ms to 26 ± 28 ms; p = NS) showed no changes. During interruption of biventricular pacing, however, both MR severity and dyssynchrony showed an acute worsening of mitral deformation indexes and parameters, reflecting global and local remodeling. Brandt et al. (25) focused specifically on the hemodynamic consequences of temporary interruption of CRT in 20 patients after a median duration of biventricular pacing of 427 days and demonstrated similar results: withdrawal of CRT resulted in a decline in LV dP/dt and an increase in MR (median MR jet area from 4.1 to 5.9 mm²; p = 0.002). However, markers of dyssynchrony were not reported in that study.

**Clinical implications.** Given the rapid increase in patients with dilated cardiomyopathy and secondary MR, on the one hand, and the poor survival of these patients on the other hand, treatment of MR is an important issue (26–28). At present, surgical valve repair or replacement is the therapy of choice, but surgery is associated with relatively high risk for perioperative morbidity and mortality, and alternative treatment options are considered in patients who are not amenable for surgery (29,30). In this perspective, the findings of the current study are relevant, because these observations suggest that CRT may be considered as a potential alternative treatment of MR in patients who cannot undergo surgery. In particular, CRT may reduce MR if dyssynchrony involves the posterior papillary muscle.

Still, it is important to emphasize that the present patients represent a highly selected cohort; 60% of patients with baseline MR did not show an acute improvement in MR. Importantly, however, these patients without an acute reduction in MR after CRT initiation had minimal APM-PPM dyssynchrony. Future prospective studies are needed to further elucidate the relation between LV dyssynchrony and reduction in MR after CRT.

**Conclusions**

Cardiac resynchronization therapy can acutely reduce MR in patients with dyssynchrony involving the papillary muscles; interruption of CRT at 6 months’ follow-up, however, resulted in acute loss of resynchronization with recurrence of MR.

**Reprint requests and correspondence:** Dr. Jeroen J. Bax, Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, the Netherlands. E-mail: jbax@ision.nl.

**REFERENCES**
