A Mechanism for Immediate Reduction in Mitral Regurgitation After Cardiac Resynchronization Therapy: Insights From Mechanical Activation Strain Mapping

Hideaki Kanzaki, MD, Raveen Bazaz, MD, David Schwartzman, MD, FACC, Kaoru Dohi, MD, L. Elif Sade, MD, John Gorcsan III, MD, FACC

Pittsburgh, Pennsylvania

OBJECTIVES

We tested the hypothesis that an immediate reduction in mitral regurgitation (MR) after cardiac resynchronization therapy (CRT) results from improved coordinated timing of the papillary muscle insertion sites, using the novel approach of mechanical activation strain mapping.

BACKGROUND

Heart failure patients with left bundle branch block often benefit acutely from CRT; however, the role and mechanism of reduction of MR are unclear.

METHODS

Twenty-six consecutive patients undergoing CRT with at least mild MR were studied (ejection fraction 24 ± 6%; QRS duration 168 ± 30 ms). Echocardiographic Doppler and strain imaging was performed immediately before and the day after CRT, as well as in 10 normal control subjects. Mechanical activation sequence maps were constructed using longitudinal strain from 12 basal and mid-LV sites, with color coding of time-to-peak strain.

RESULTS

Mitral regurgitation by the volumetric method consistently decreased after CRT: regurgitant volume from 40 ± 20 ml to 24 ± 17 ml and regurgitant fraction from 40 ± 12% to 25 ± 14% (both: p < 0.001 vs. baseline). Normal controls had uniform segmental time-to-peak strain, with a difference of only 12 ± 8 ms between all segments. In contrast, CRT patients at baseline had a 106 ± 74 ms time delay between papillary muscle insertion sites (p < 0.001 vs. normal). This interpapillary muscle time delay shortened after CRT to 39 ± 43 ms (p < 0.001 vs. baseline) and was significantly correlated with reductions in mitral regurgitant fraction (r = 0.77, p < 0.001).

CONCLUSIONS

Cardiac resynchronization therapy significantly and immediately reduced MR. Improved coordinated timing of mechanical activation of papillary muscle insertion sites appears to be a mechanistic contributor to immediate MR reduction by CRT. (J Am Coll Cardiol 2004; 44:1619–25) © 2004 by the American College of Cardiology Foundation

Cardiac resynchronization therapy (CRT) can improve heart failure (HF) symptoms, exercise capacity, and potentially survival in patients with HF and left bundle branch block (LBBB) (1–3). These benefits have been mainly attributed to increased efficiency of left ventricular (LV) filling and ejection through improvements in atrioventricular (AV) coupling and intraventricular synchronzation as well as interventricular synchronzation (4–9). Although these beneficial findings may hypothetically be associated with a reduction in mitral regurgitation (MR) after CRT, a clear distinction has not been defined between immediate MR reduction and remote decreases secondary to reverse remodeling of the LV, which takes from weeks to months to occur. Furthermore, the mechanism of immediate reduction in MR remains unclear. Our objectives were to quantitatively evaluate the reduction in MR immediately after CRT using the volumetric Doppler method and to test the hypothesis that the MR reduction was mechanistically associated with improved coordination of the LV segments containing papillary muscles, using the novel approach of strain mechanical activation mapping.

METHODS

Subjects. Of 33 consecutive patients undergoing CRT, 26 were selected. Five were excluded because they had no MR, and two were excluded because of technically inadequate images for strain analysis. The protocol was approved by the Human Research Institutional Review Board. The subjects' mean age was 66 ± 10 years (21 males); all had chronic, moderate to severe HF (New York Heart Association class III or IV) despite optimal standard medical therapy, LVEF <35%, and QRS duration >120 ms. Their mean ejection fraction (EF) was 24 ± 6%; the QRS duration was 168 ± 30 ms (all with LBBB); and the PR interval was 194 ± 38 ms. Heart failure was attributed to coronary artery disease (n = 19) or nonischemic cardiomyopathy (n = 7) by normal coronary angiography. No patients had greater than mild aortic regurgitation or atrial fibrillation. Ten normal subjects...
with no history of cardiovascular disease and normal complete echocardiographic Doppler studies (58 ± 11 years, 4 males, QRS 90 ± 10 ms, LVEF 64 ± 5%) served as controls.

Cardiac resynchronization therapy was initiated with implantation of a biventricular pacing system (CONTAK CD Models 1823, H115 or RENEWAL Model H135, Guidant Corp., St. Paul, Minnesota; InSync ICD Model 7272 or Marquis Model 7277, Medtronic, Minneapolis, Minnesota), a right ventricular apical lead, and a LV pacing lead positioned in a LV epicardial vein via the coronary sinus. The LV pacing lead placement was lateral in 11, posterolateral in eight, anterior in three, anterolateral in three, and posterior in one.

**Echocardiography.** All echocardiographic studies were performed using either the GE-Vingmed Vivid 5 or 7 system (GE Vingmed Ultrasound, Horten, Norway). The LV volumes and EF were assessed by the modified biplane Simpson’s method (10). Color Doppler echocardiography was performed with an aliasing velocity of 55 cm/s (Fig. 1) (11). The onset and duration of MR were determined on color M-mode echocardiograms. The diastolic filling time was measured as the time interval of mitral inflow profile derived from pulsed-wave Doppler echocardiography. Color-coded tissue Doppler cine loops from three beats were obtained from three apical views: four-chamber, two-chamber, and long-axis views at depths of 14 to 18 cm. The pulse repetition frequency was 1 kHz; the velocity range was ±16 cm/s; and the frame rate was 77 to 134 Hz. Baseline and postprocedural assessment was achieved immediately before and the day after initiation of CRT.

**Quantification of MR.** The severity of MR was quantified with the volumetric method, as previously described elsewhere in detail (12). Briefly, MR regurgitant volume was obtained as the mitral inflow stroke volume minus the LV outflow stroke volume. The mitral inflow and LV outflow stroke volumes were determined as the cross-sectional area of mitral and aortic annuluses multiplied by the pulsed-wave Doppler time–velocity integral at the annular level, respectively: stroke volume = 1/4 π (diameter)² (time-velocity integral). Diameters of the mitral annulus were measured at the base of the leaflets at the time of maximum valvular opening from the apical four- and two-chamber views and aortic annular diameter from the parasternal long-axis view. The MR regurgitant fraction was obtained by dividing the regurgitant volume by mitral inflow volume.

**Mechanical activation with strain mapping.** To assess the LV sequence of mechanical activation, isochronal mapping was performed using strain measurements (13,14). Strain was calculated with commercially available software EchoPAC PC version 3.00 (GE Vingmed Ultrasound) from the velocity data set. Regions of interest with the initial length of 12 mm were placed in basal and mid segments from each view, for a total of 12 segments, to measure the interval from the onset of the Q-wave on the electrocardiogram to the peak longitudinal systolic strain. To assist in the understanding of the propagating mechanical activation time wave front, a modified “bull’s-eye” format included basal and mid-LV segments (Figs. 2 and 3)

**Figure 1.** An example of acute reduction in mitral regurgitation by color Doppler before (left) and immediately after (right) cardiac resynchronization therapy.
Isochrones were manually interpolated and color-coded using a multi-color map with 50-ms increments.

**Statistical analysis.** For each measurement, a minimum of three cardiac cycles was averaged. Continuous data are presented as the mean value ± SD and compared with the two-tailed Student $t$ test for paired and unpaired data, as appropriate. Linear regression analysis was used to identify the relationship between two groups. Intraobserver and interobserver variabilities were analyzed in 10 randomly selected studies and expressed as the mean percent error (difference divided by number of observations). Statistical significance was assumed for $p < 0.05$. All statistical analyses were performed using StatView 5.0 for Windows (SAS Institute, Cary, North Carolina).

**RESULTS**

**Quantitative Doppler echocardiography.** Baseline group mean MR regurgitant volume was $40 ± 20$ ml, and regurgitant fraction was $40 ± 12\%$. After CRT, the MR regurgitant volume decreased to $24 ± 17$ ml and regurgitant fraction decreased to $25 ± 14\%$ (both: $p < 0.001$ vs. baseline) (Fig. 4). The MR associated with LBBB by color Doppler characteristically occurred early in the cardiac cycle, with an

**Figure 2.** Echocardiographic strain images from the four-chamber view and two-chamber view, with corresponding time-strain plots from sites adjacent to papillary muscles before and after cardiac resynchronization therapy. Baseline plots demonstrate late peak strain occurring in the anterolateral papillary muscle site compared with the posteromedial papillary muscle site. Peak strain is aligned after cardiac resynchronization therapy in these sites.

**Figure 3.** Construction of bull’s-eye plot from multiple time-strain curves from the basal and mid-ventricular levels, demonstrating the anatomic location of papillary muscles in a “bull’s-eye” plot.
onset of 38 ± 47 ms from the beginning of the QRS complex, with a duration of 288 ± 129 ms at baseline. After CRT, MR appeared to occur later (70 ± 52 ms) after the onset of the QRS complex, and the duration decreased to 188 ± 126 ms (p < 0.002). Heart rate was not changed (72 ± 10 min⁻¹ to 74 ± 10 min⁻¹). Other observed changes included decreases in peak E-wave velocity from 88 ± 31 cm/s to 80 ± 24 cm/s (p < 0.05), prolongation of E-wave deceleration time from 139 ± 37 ms to 164 ± 41 ms (p < 0.001), and increases in diastolic filling time from 357 ± 92 ms to 408 ± 102 ms (p < 0.05). After CRT, LV end-diastolic volume did not change (238 ± 78 ml to 235 ± 75 ml), but end-systolic volume decreased from 182 ± 64 ml to 175 ± 60 ml (p < 0.001), and EF increased slightly from 24 ± 6% to 26 ± 6% (p < 0.005). The mitral annular diameter remained unchanged (3.3 ± 0.3 cm and 3.3 ± 0.3 cm). The cardiac index of forward flow increased by 20 ± 21% after CRT (2.0 ± 0.4 l/min/m² to 2.3 ± 0.5 l/min/m², p < 0.001). Increases in stroke volume were correlated with reduction of regurgitant volume (r = 0.46, p < 0.05) and regurgitant fraction (r = 0.67, p < 0.001). After CRT, the average AV delay was 124 ± 12 ms, using standard values, and formal echocardiographic Doppler AV or interventricular optimization studies were not performed.

**Strain mechanical activation mapping.** Representative examples of mapping the timing of mechanical activation at baseline and after CRT in representative patients with native LBBB and right ventricular pacing appear in Figure 5. In 19 (74%) of 26 patients, mechanical activation occurred first in the segment with the posteromedial papillary muscle insertion and was delayed in the segment with the anterolateral papillary muscle insertion and was the typical LBBB pattern. Mechanical activation from pooled data at baseline before CRT revealed a significant intrapapillary activation delay of 106 ± 74 ms, as compared with normal controls, which was only 12 ± 8 ms (p < 0.001). The interpapillary muscle activation time delay shortened to 35 ± 31 ms after CRT (p < 0.001 vs. baseline). Shortening of this mechanical time delay between the LV segments adjacent to the papillary muscles was significantly correlated with a reduction of the MR regurgitant fraction (r = 0.77, p < 0.001) (Fig. 6). It should be noted that none of the 19 patients with ischemic cardiomyopathy had scar, as supported by a thin and akinetic wall adjacent to the papillary muscles. To further support the validity of the strain mechanical activation map, LV lead placement after CRT was associated with the actual or immediately adjacent anatomic segment with the shortest time to peak strain in all but one patient (96%).

**Reproducibility.** Interobserver and intraobserver variabilities were 9.5 ± 4.6% and 7.5 ± 4.5% for MR regurgitant volume, 6.1 ± 3.6% and 6.3 ± 2.2% for regurgitant fraction, and 5.8 ± 7.3% and 4.3 ± 5.0% for time to peak strain, respectively.

**DISCUSSION**

This is the first study to quantify and associate the immediate reduction in MR after CRT with the coordinated mechanical activation of papillary muscle insertion sites, providing mechanistic insight. The volumetric Doppler method was used to quantify MR, and the novel method of strain mechanical activation mapping was used to assess papillary muscle tethering sequence. Although reductions in MR may result from alterations in any part of the mitral apparatus, including leaflets, chordae, annulus, or papillary muscles, the present study demonstrates no immediate change in mitral annular dimensions and identifies the interpapillary muscle activation time delay as a principal factor related to MR in patients with HF and LBBB that is immediately improved with CRT in a significant proportion of patients.

Other mechanisms of decreased MR after CRT have previously been attributed to decreases in LV size from reverse remodeling, which requires weeks to months to occur. In the MUSTIC study, the MR jet area by color Doppler was observed to decrease from 7.4 ± 6.8 cm² to 5.6 ± 8.3 cm² in six months (1). In the MIRACLE study, the MR jet area decreased from a median of 7.31 ± 6.14 cm² to 2.1 cm² at six-month follow-up (3). Observations of more acute reductions in MR have been made by Yu et al. (2), who reported that the MR jet area/left atrial area decreased from 36 ± 19% to 21 ± 17% one week after CRT. These and other previous studies have assessed MR severity by color Doppler (1–3,16). However, color jets are considerably affected by numerous factors: transducer frequency, gain, Nyquist limit, frame rate, jet eccentricity, and flow momentum, which is the product of flow rate and velocity (17–21). Breithardt et al. (16) assessed the degree of MR using the proximal isovelocity surface area method, which uses both color and spectral Doppler data, during both pacing-off and CRT in the first week after CRT, and reported a significantly reduced regurgitant volume from 32 ± 19 ml to 19 ± 9 ml and effective regurgitant orifice area from 25 ± 19 mm² to 13 ± 8 mm² with CRT. Although eccentric MR jets by color Doppler accentuated in early or
pre-systole and multiple MR jets, which interfere with color Doppler quantification, were often observed in our study population, the volumetric method was feasible to quantify the MR reduction in all. Nonetheless, our present results support these previous findings of a reduction in MR after CRT and extend these observations to include a more

Figure 5. Mechanical activation maps in the “bull’s-eye” projection from representative heart failure patients before and after cardiac resynchronization therapy (CRT). (A) A patient with LBBB. (B) A patient who previously received a right ventricular pacer (RV) for bradycardia and was RV paced at baseline. Time to peak systolic strain was color coded with lines representing isochrones of mechanical activation times at 50-ms intervals. The X indicates sites of lead placement, and the arrow indicates the direction of the propagating mechanical activation. Time to peak strain of sites adjacent to anterolateral (AL P) and posteromedial (PM P) papillary muscles are shown. A decrease in interpapillary muscle time delay was associated with decreased mitral regurgitation (MR).

Figure 6. Pooled data demonstrating reductions in interpapillary muscle activation delay (left) from before to after cardiac resynchronization therapy (CRT). This was calculated as the difference between time to peak strain in papillary muscle sites. The change in interpapillary muscle activation delay after CRT (right) was significantly correlated with decreases in mitral regurgitant fraction.
immediate time frame and to provide mechanistic insight with strain mechanical activation mapping.

Another potential contributor to MR in LBBB is prolongation of isovolumic contraction time (22). As a result of the development of a LV-left atrial reverse pressure gradient when atrial contraction is not followed by an appropriately timed ventricular systole, diastolic MR is more likely with the incomplete mitral valve closure (23). Nishimura et al. (7) reported that a reduction in diastolic MR was a crucial benefit from AV sequential pacing. As Breithardt et al. (16) proposed, CRT can restore the mechanical AV synchrony and increase LV contraction efficiency, thereby generating the effective transmirtal closing force. Indeed, in our results, MR duration shortened by 41 ± 23% (maximum 86%), whereas the period (from mitral valve closing to re-opening) when MR can occur shortened by 13 ± 10% (maximum 35%) after CRT. These findings agree with their concept that the transmirtal pressure gradient mediated by a rate of rise in LV pressure (dP/dtmax) after CRT causes a reduction of MR.

Our sequence mapping with strain imaging revealed that the mechanical activation time delay between LV segments adjacent to the papillary muscles was associated with development of MR. This suggests that MR in LBBB relates to an altered systolic balance of forces acting on papillary muscle due to uncoordinated regional LV activation in these segments, which results in geometric changes in mitral leaflet attachments. In experimental models, functional MR has been shown to occur because of a posterior shift of the papillary muscle combined with annular dilation (24–26). Otsuji et al. (27) and Hung et al. (28) demonstrated the importance of papillary muscle tethering forces as mechanically related to MR. We observed a delay in peak strain at the mid lateral segment adjacent to the anterolateral papillary muscle, implying tethering of the mitral leaflet, which was improved immediately after CRT. In other words, CRT appears to coordinate the tethering forces on the papillary muscles and increase the leaflet coaptational surface to reduce MR in these patients. Although alterations in annular size and shape may also contribute to MR reduction, no significant change in mitral annular size was observed, and intrapapillary muscle activation appears to be a significant factor (28–33).

Study limitations. Changes in blood pressure may potentially affect the MR data. However, because no alterations in medications that affect blood pressure were made from before to after CRT, it is unlikely that was a significant limitation. Another limitation is that this study focused on immediate MR and LV functional measures after CRT. Assessment of patients’ symptoms or quality of life was not part of the study, and longer term effects on morbidity and mortality warrant further investigation. A technical limitation is that strain measurements are angle-dependent; however, the use of time-to-peak measures or angle correction may minimize this problem (13,14,34,35). Thus, we used mechanical activation times from the three different apical views, which could not be simultaneously acquired to construct the activation maps. We did not observe a significant variation in beat-to-beat cardiac cycle length, but the mapping approach may have limitations in patients with an irregular rhythm, in particular atrial fibrillation.

Acknowledgments
The authors thank Leonald I. Ganz, MD, William W. Barrington, MD, Samir F. Saba, MD, Ogundu Ngwu, MD, and Walter L. Atiga, MD, for their clinical expertise and cooperation. We thank Donald Severyn, MS, for technical assistance. We also gratefully acknowledge the help and cooperation of the Electrophysiology Study Laboratory technicians and nurses.

Reprint requests and correspondence: Dr. John Gorcsan III, University of Pittsburgh, Scaife S564, 200 Lothrop Street, Pittsburgh, Pennsylvania 15213-2582. E-mail: gorcsanj@msx.upmc.edu.

REFERENCES


