Acute Effects of Cardiac Resynchronization Therapy on Functional Mitral Regurgitation in Advanced Systolic Heart Failure

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OBJECTIVES We studied the acute effects of cardiac resynchronization therapy (CRT) on functional mitral regurgitation in heart failure (HF) patients with left bundle branch block (LBBB).

BACKGROUND Both a decrease in left ventricular (LV) closing force and mitral valve tethering have been implicated as mechanisms for functional mitral regurgitation (FMR) in dilated hearts. We hypothesized that an increase in LV closing force achieved by CRT could act to reduce FMR.

METHODS Twenty-four HF patients with LBBB and FMR were studied after implantation of a biventricular CRT system. Acute changes in FMR severity between intrinsic conduction (OFF) and CRT were quantified according to the proximal isovelocity surface area method by measuring the effective regurgitant orifice area (EROA). Results were compared with the changes in estimated maximal rate of left ventricular systolic pressure rise (LV+dp/dt_max) and transmitral pressure gradients (TMP), both measured by Doppler echocardiography.

RESULTS Cardiac resynchronization therapy was associated with a significant reduction in FMR severity. Effective regurgitant orifice area decreased from 25 ± 19 mm² (OFF) to 13 ± 8 mm² (CRT). The change in EROA was directly related to the increase in LV+dp/dt_max (r = −0.83, p < 0.0001). Compared with OFF, TMP increased more rapidly during CRT, and a higher maximal TMP was observed (OFF 73 ± 24 mm Hg vs. CRT 85 ± 26 mm Hg, p < 0.01).

CONCLUSIONS Functional mitral regurgitation is reduced by CRT in patients with HF and LBBB. This effect is directly related to the increased closing force (LV+dp/dt_max). The results support the hypothesis that an increase in TMP, mediated by a rise in LV+dp/dt_max due to more coordinated LV contraction, may facilitate effective mitral valve closure. (J Am Coll Cardiol 2003;41:765–70) © 2003 by the American College of Cardiology Foundation

Functional mitral regurgitation (FMR) in dilated cardiomyopathy (DCM) results from an imbalance between the closing and the tethering forces that act on the mitral valve leaflets (1). Ventricular dilation and increased chamber sphericity increase the distance between the papillary muscles to the enlarged mitral annulus as well as to each other, restricting leaflet motion and increasing the force needed for effective mitral valve closure (1–4). This mitral valve closing force is determined by the systolic left ventricular (LV)-left atrial pressure difference, that is, the transmitral pressure gradient (TMP). In vitro studies have demonstrated that increasing TMP can decrease the effective regurgitant orifice area (EROA), but isolating this effect is difficult in the clinical and even in the experimental setting. Recoordination of LV contraction by cardiac resynchronization therapy (CRT) with biventricular pacing may increase the maximal rate of LV systolic pressure rise (LV+dp/dt_max) (5) and, thus, increase TMP acutely (6). Therefore, it offers a unique opportunity to study the effect of an acute increase in TMP on mitral valve competence, irrespective of loading conditions and reverse remodeling, which may occur during chronic pacing therapy. We hypothesized that CRT increases LV+dp/dt_max and, consequently, TMP and, thus, decreases mitral valve EROA. This was tested in a consecutive group of patients with severe LV dysfunction, left bundle branch block (LBBB), and FMR using continuous wave (CW) Doppler echocardiography and color Doppler flow mapping of the proximal flow convergence region.

METHODS Patients. We studied 24 consecutive patients presenting with severely impaired LV systolic function (transthoracic biplane ejection fraction [EF] <30%), LBBB (QRS >120 ms), and FMR measured by color Doppler echocardiography. All patients received a biventricular pacing device for CRT with a right ventricular apical lead and LV pacing electrodes implanted through the coronary sinus and positioned in an LV epicardial vein. Informed consent was obtained from all patients before the echocardiographic examination with acute reprogramming of the pacemakers.

Echocardiography protocol. Transthoracic echocardiography was performed in the first week after implantation of the CRT system or before the onset of active CRT. All patients underwent a standard two-dimensional and Doppler echocardiographic examination at rest in the left lateral supine position during intrinsic conduction, no pacing (OFF) and CRT. Left ventricular end-diastolic volume (ml), end-systolic volume (ml), and EF (%) were measured...
Abbreviations and Acronyms

- CAD = coronary artery disease
- CRT = cardiac resynchronization therapy
- CW = continuous wave
- DCM = dilated cardiomyopathy
- EF = ejection fraction
- EROA = effective regurgitant orifice area
- FMR = functional mitral regurgitation
- LBBB = left bundle branch block
- LV = left ventricle/ventricular
- LV+dp/dt_max = maximal rate of left ventricular systolic pressure rise
- MRV_max = maximal velocity of the mitral regurgitant jet obtained by continuous wave Doppler
- MRVTI = mitral regurgitant velocity time integral
- OFF = intrinsic conduction, no pacing
- PISA = proximal isovelocity surface area
- RegFlow = regurgitant flow
- RegVol = regurgitant volume
- TMP = transmitral pressure gradient
- TMP100 = transmitral pressure gradient 100 ms after onset of the functional mitral regurgitation jet
- TMP_max = maximal transmitral pressure gradient
- V_alias = aliasing velocity
- FMR, excluding any presystolic mitral regurgitation.

RESULTS

Clinical patient characteristics are presented in Table 1. All patients were in stable sinus rhythm. Ventricular pacing was performed in an atrial triggered mode with a mean atrioventricular delay of 109 ± 18 ms. Biventricular pacing acutely decreased mitral regurgitation severity and improved LV systolic function as measured by LV+dp/dt_max and EF, with no change in heart rate (Table 2). In 23 of 24 patients, EROA decreased (Fig. 2), and ΔEROA was directly related to the increase in ΔLV+dp/dt_max (Fig. 3). The improved LV+dp/dt_max resulted in an increase of TMP_max from 73 ±
LV chamber sphericity was documented by a sphericity ease (CAD) and with DCM forences observed between patients with coronary artery dis-

There were also no signiicant differ-

24 mm Hg (OFF) to 85 ± 26 mm Hg (CRT, p < 0.01 vs. OFF) and of TMP100 from 41 ± 17 mm Hg (OFF) to 61 ± 18 mm Hg (CRT, p < 0.0001 vs. OFF). A signiicant, although weak, linear correlation was found between ΔEROA and ΔTMP100 (ΔEROA = −0.54 × ΔTMP100 −24.8, r = −0.44, p = 0.03), but not between ΔEROA and ΔTMPmax (ΔEROA = −0.57 × ΔTMPmax −33.8, r = −0.2, p = NS). The duration of FMR decreased from 478 ± 77 ms (OFF, 62 ± 12% of cycle length) to 444 ± 57 ms (CRT, 57 ± 8% of cycle length, p = 0.02 vs. OFF).

No signiicant relationship was observed between baseline FMR severity and end-diastolic volume, QRS width, and LV sphericity index. There were also no signiicant differences observed between patients with coronary artery disease (CAD) and with DCM for ΔEROA (DCM: 48 ± 21% vs. CAD: 31 ± 25%, p = NS) and for ΔLV+dP/dtmax (DCM: 46 ± 28% vs. CAD: 40 ± 28%, p = NS). Increased LV chamber sphericity was documented by a sphericity index of 0.56 ± 0.13, but was not signiicantly affected by CRT (0.58 ± 0.14, p = NS vs. OFF). Midsystolic mitral leaflet tenting area was smaller during CRT (6.21 ± 2.04 cm2 [OFF] vs. 5.52 ± 1.72 cm2 [CRT], p = 0.02). There was no signiicant correlation between the mitral leaflet tenting area and EROA.

Inter- and intraobserver variability. The mean percent errors for measurements of Doppler time intervals and velocities were 3 ± 2% and 4 ± 2% for the same observer and 5 ± 3% and 5 ± 4% between two blinded observers. For measurement of the PISA radius, the intra- and interobserver variabilities were 6 ± 5% and 7 ± 5%, respectively.

DISCUSSION

The present study demonstrates that CRT can acutely reduce the severity of FMR in heart failure patients with an LBBB, irrespective of the potential long-term reverse re-modeling effect on LV shape and size (12,13). Furthermore,

Table 1. Clinical Characteristics of the Study Population (n = 24)

<table>
<thead>
<tr>
<th>Gender (male/female)</th>
<th>19/5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>63 ± 10</td>
</tr>
<tr>
<td>CAD/DCM</td>
<td>12/12</td>
</tr>
<tr>
<td>NYHA functional class (III/IV)</td>
<td>23/1</td>
</tr>
<tr>
<td>PR interval (ms)</td>
<td>181 ± 41</td>
</tr>
<tr>
<td>QRS width (ms)</td>
<td>176 ± 25</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>259 ± 98</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>208 ± 90</td>
</tr>
<tr>
<td>EF (%)</td>
<td>21 ± 6</td>
</tr>
</tbody>
</table>

Plus minus values are means ± SD.

CAD = coronary artery disease; DCM = dilated cardiomyopathy; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; NYHA = New York Heart Association.

Table 2. Effects of CRT on Echocardiographic Parameters

<table>
<thead>
<tr>
<th></th>
<th>No CRT</th>
<th>CRT</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>79 ± 14</td>
<td>78 ± 13</td>
<td>p = NS</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>259 ± 98</td>
<td>263 ± 98</td>
<td>p = NS</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>208 ± 90</td>
<td>198 ± 85</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>EF (%)</td>
<td>21 ± 6</td>
<td>26 ± 9</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>RegFlow (cm²/s)</td>
<td>100 ± 67</td>
<td>59 ± 35</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>EROA (mm²)</td>
<td>25 ± 19</td>
<td>13 ± 8</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>RegVol (ml/beat)</td>
<td>32 ± 19</td>
<td>19 ± 9</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>LV+dP/dtmax (mm Hg/s)</td>
<td>634 ± 349</td>
<td>867 ± 396</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

CRT = cardiac resynchronization therapy; EDV = end-diastolic volume; EF = ejection fraction; EROA = effective regurgitant orifice area; ESV = end-systolic volume; LV+dP/dtmax = maximal rate of left ventricular systolic pressure rise; RegFlow = regurgitant flow; RegVol = regurgitant volume.
the reduction in FMR is quantitatively related to an increase in LV+dP/dt_{max} and TMP. We observed an immediate reduction in mean EROA and RegVol of about 40% by CRT.

**Mechanistic insights.** Prior studies demonstrated that the presence of FMR in heart failure is strongly dependent on alterations in LV shape, as the tethering forces that act on the mitral leaflets are higher in dilated, more spherical ventricles (14). These geometric changes alter the balance between tethering and closing forces and impede effective mitral valve closure. Under these conditions, the mitral regurgitant orifice area will be largely determined by the phasic changes in TMP (15–17), and worsening of LV dysfunction with a delayed LV rate of pressure rise will further increase FMR severity due to the impaired closing force. Consequently, it has been suggested that therapeutic interventions aimed to improve TMP should be able to reduce FMR severity (17). Our study represents a direct therapeutic application of this concept and demonstrates that an increase in TMP, mediated by a rise in LV+dP/dt_{max}, may oppose the increased mitral leaflet tethering forces in DCM and facilitate more effective mitral valve closure. Cardiac resynchronization therapy caused both an increase in peak transmitral closing force (TMPmax) as well as an accelerated rise in TMP during the isovolumic contraction phase, as reflected by the increase in TMP_{100}. The accelerated rise in TMP effectively counteracted the increased tethering forces that impair mitral valve competence (Fig. 4) and decreased acutely mid-systolic mitral leaflet tenting area.

**Cause-effect relationship of increase in dP/dt and decrease in EROA.** In normal subjects, LV+dP/dt_{max} drops abruptly with aortic valve opening, as contraction is translated into moving blood rather than raising pressure. It could, therefore, be argued that in patients with mitral regurgitation the decrease in EROA by CRT might have raised LV+dP/dt_{max} by preventing early ventricular contraction force to be translated into motion (regurgitation) instead of pressure. In this case, the increase in LV+dP/dt_{max} would be the effect rather than the cause of a decrease in EROA. However, animal experiments in which ischemic mitral regurgitation was abolished by chordal cutting (18) have not found any significant change in LV+dP/dt_{max}. We, therefore, believe that CRT increases LV+dP/dt_{max}, which, in turn, decreases EROA. The concept that the Doppler-derived LV+dP/dt_{max} which represents the rate of rise of the LV-left atrial pressure difference, is the cause (rather than the effect) of the decrease in EROA is further supported by experimental studies, which have demonstrated that the rate of rise of the transmitral closing force effectively determines the size of the EROA (17).

**Influence of LV geometry on FMR severity.** The fact that LV sphericity, which was pathologic in all our patients, was not acutely affected by CRT further underscores the notion that the reduction in EROA was independent of a change in LV geometry. However, such a reverse remodeling process may be observed chronically and, thus, may contribute to a further decrease in FMR severity by CRT (2).

Although systolic mitral valvular tenting is a major determinant of EROA, we found no significant correlation between mitral deformation and FMR severity in our patient population, which is in contrast with previous reports (2). This apparent disagreement might be explained by the high prevalence of ventricular asynchrony in our study as we included only patients with significant electrical

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**Figure 2.** Individual changes in effective regurgitant orifice area (EROA) (mm²) between baseline (OFF) and cardiac resynchronization therapy (CRT); EROA showed a wide range during OFF and decreased with CRT in 23 patients. A small increase in EROA was observed in one patient with mild regurgitation during OFF (dashed line).

**Figure 3.** The decrease in effective regurgitant orifice area (EROA), displayed as the percent change between OFF and cardiac resynchronization therapy (CRT), was directly correlated to the increase in left ventricular systolic function, as measured by the percent increase in maximal rate of left ventricular systolic pressure rise (LV+dP/dt_{max}):

$$\Delta \text{EROA} = -0.7 \times \Delta \text{LV+dP/dt}_{max} - 7.6, r = -0.83, p < 0.0001.$$
study limitations

The applied PISA method assumes that the convergence zone is hemispherical. Recent studies have demonstrated that mitral valve orifice shape is rather elliptic or slit-like (28). Although a hemielliptical formula may, therefore, be more suitable to describe this situation than a simplified hemispherical formula, the current method has been extensively validated in the clinical setting and found to be both accurate and reproducible (29). Moreover, because we focused on the intraindividual changes in FMR with CRT, this limitation is unlikely to have affected the principle results of the study. Although the mitral regurgitant orifice is dynamic (15,16), midsystolic EROA appears to be a robust surrogate of mean EROA (30).

Estimation of LV dP/dt max with the described CW Doppler technique tends to underestimate true LV+ dP/dt max because it calculates the mean rise in LV pressure during the isovolumic contraction phase rather than the true maximum instantaneous pressure rise (31). Despite this small systematic error, the method is reproducible and even valuable for the prediction of prognosis in patients with dilative cardiomyopathy and CRT (32).

We did not systematically measure arterial blood pressure in this study, and, thus, no direct conclusions can be made on the possible changes in left atrial pressure. However, it is most likely that the measured increase in TMP max reflects the previously observed increase in systolic arterial blood pressure with CRT (5,6). Our study is, furthermore, limited to acute measurements, and no conclusions can be drawn concerning the long-term effects of CRT on FMR severity. This has been studied by previous researchers, who demonstrated that long-term CRT may reduce FMR severity (33,34).

Conclusions

Cardiac resynchronization therapy in selected patients with advanced heart failure and electrical conduction delay acutely reduces the severity of FMR by decreasing the EROA. This effect is directly related to an improvement in LV systolic function causing an accelerated rise in TMP, which effectively counteracts the increased tethering forces that impair mitral valve competence. The acute effect is

Figure 4. Schematic representation of the relationship between the increase in transmural pressure gradient (TMP) (the instantaneous difference between left ventricular and left atrial pressure) and the decrease in effective regurgitation orifice area (EROA). During OFF (top panel), left ventricular (LV) contractility is low and results in a slow rise in the LV pressure curve and TMP with a relatively late systolic maximum. Due to the slow LV pressure rise with delayed development of an effective transmural closing force (approximately TMP), EROA remains large for a relatively long period until it finally reaches its minimal value. In contrast, during cardiac resynchronization therapy (CRT) (bottom panel), LV contractility improves, TMP rises faster and to a higher maximal value, which is also reached earlier. Consequently, the reduction in EROA occurs earlier, EROA reaches lower values and for a prolonged period of time. The shaded area represents the time in systole during which EROA is below 50% of its initial value. Note that, in the chosen example, the reduction in the height of the V-wave after a decrease in the initial mitral regurgitation will contribute to a preserved TMP during the latter half of systole. Solid line = left atrial (LA) and LV pressure; dotted line = EROA. Adapted from Hung et al. (15).
independent from geometrical changes (reverse remodeling) and may exert further beneficial effects on FMR severity.

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