OBJECTIVES
The aim of this study was to investigate the relationship between dynamics of functional mitral regurgitation (MR) and the degree of electrical conduction disturbance, and to evaluate the impact of cardiac resynchronization therapy (CRT) on MR severity and its phasic pattern.

BACKGROUND
Mechanisms of phasic changes of functional MR, which may be determined by annulus dilation and tethering of the leaflet, remain unclear.

METHODS
Transthoracic two-dimensional echocardiography was performed in 60 patients with functional MR. A biventricular pacemaker was implanted in 19 patients. The mitral annulus area (MAA) and the tenting area (TA) were measured from apical views. The MR volume and fraction were assessed by the quantitative pulsed Doppler method. Instantaneous regurgitation flow rate was measured by proximal flow convergence method. A dynamic change in MR flow rate was evaluated by frame-by-frame analysis throughout systole.

RESULTS
A phasic pattern with two peaks at early- and late-systole and decrease in mid-systole was noticed in 57 patients. The early-systolic peak of MR was larger than the late-systolic peak (128.4 ± 64.3 ml/s vs. 73.9 ± 55.1 ml/s, p < 0.001). The ratio of flow rate at these two peaks correlated with QRS duration (r = 0.55, p < 0.001). Early-systolic flow rate reduced after CRT (143.9 ± 60.8 ml/s to 90.7 ± 54.1 ml/s, p < 0.05), but late-systolic flow rate did not (61.5 ± 55.0 ml/s to 51.2 ± 40.9 ml/s, p = NS). A similar pattern was observed for TA, whereas MAA did not change after CRT.

CONCLUSIONS
Biphasic pattern was found in functional MR, and the ratio of flow rate at two peaks correlated with QRS duration. The CRT decreased regurgitation flow volume by reducing early-systolic MR but not late-systolic MR, resulting in the change in phasic pattern of functional MR. (J Am Coll Cardiol 2005;46:2270–6) © 2005 by the American College of Cardiology Foundation

Functional mitral regurgitation (MR) is a common and morbid complication in patients with ischemic heart disease or dilated cardiomyopathy, increasing long-term risk and mortality (1–4). Several competing geometric and hemodynamic factors may cause the functional MR: mitral annulus dilation, tethering of the leaflet secondary to papillary muscles dislocation, and ventricular dysfunction with reduced transmitral pressure acting to close the leaflets (5–9). Importantly, these factors vary throughout a cardiac cycle, leading to dynamic changes in functional MR during the regurgitation period (10–14). Previous studies reported that a biphasic pattern with early- and late-systolic peaks and a mid-systolic decrease of regurgitation flow was observed in patients with functional MR (12,14). Although this phenomenon may have the potential to provide insights into important aspects of mechanisms and therapeutic target of functional MR, it is relatively ignored.

Cardiac resynchronization therapy (CRT) has been recently introduced as a complementary treatment option to improve ventricular synchrony, resulting in increased ventricular function (15–19) as well as reduced MR (18–22). In recent investigations of the mechanism of reduced MR after CRT, transmitral pressure (20) and mechanical activation of papillary muscle insertion regions (21), which determine the severity of MR (5,6,8) and its time variation (12,14), were altered by CRT in patients with functional MR. Decrease of regurgitation flow after CRT might occur with concurrent changes of its dynamics. In addition, the degree of coordination of the regional ventricular wall activation might relate to the severity of MR and/or its phasic pattern. The purpose of this study was therefore to investigate the relationship between dynamics of MR and the degree of electrical conduction disturbance, and to evaluate the impact of CRT on the overall severity of MR and its phasic pattern.

METHODS
Study population. Seventy-four patients with functional MR who underwent transthoracic two-dimensional echocardiography were initially enrolled in this study. The patients with a history of cardiac surgery (n = 1), permanent atrial fibrillation (n = 5), evident intrinsic abnormality of the mitral valve (n = 2), and poor image quality of echocardiography (n = 6) were excluded. The final study group
Abbreviations and Acronyms

CRT = cardiac resynchronization therapy  
EDV = end-diastolic volume  
EF = ejection fraction  
ESV = end-systolic volume  
LV = left ventricle  
MAA = mitral annulus area  
MR = mitral regurgitation  
PFC = proximal flow convergence  
TA = tenting area

Consisted of 60 patients (44 males, mean age 60 ± 10 years). Eighteen had idiopathic dilated cardiomyopathy, and 42 patients had a history of myocardial infarction (20 in the anterior wall, 17 in the inferoposterior wall, and 5 in both the anterior and inferoposterior walls). Echocardiography documented left ventricular (LV) dysfunction in all patients with a mean LV end-diastolic volume (EDV) of 312.4 ± 126.0 ml, a mean end-systolic volume (ESV) of 242.3 ± 107.5 ml, and a mean LV ejection fraction (EF) of 23.5 ± 7.7%. The patients had either a normal sinus rhythm (n = 58) or had a pacemaker-induced rhythm (n = 2) with a mean QRS duration of 138.5 ± 39.5 ms (range 74 to 222 ms) on 12-lead surface electrocardiogram.

A biventricular pacemaker was implanted in 19 of 60 patients (15 males, mean age 64 ± 9 years) according to the recommendation of the patient’s attending physicians, independent of the results of the present study. The mean QRS duration was 161.6 ± 33.3 ms before biventricular pacemaker implantation, and transthoracic two-dimensional echocardiography was obtained before and >3 months after biventricular pacemaker implantation (241 ± 187 days). All patients received a biventricular pacing system with a right ventricular apical lead and LV pacing electrodes implanted through the coronary sinus and positioned in a LV epicardial vein (15 in a lateral position and 4 in a posterior position). The study was approved by the ethics committee at our institution.

Transesophageal two-dimensional echocardiography. Transesophageal two-dimensional echocardiography was performed with a Sonos 5500 (Philips Medical Systems, Andover, Massachusetts) or a Vivid 7 (GE Medical Systems, Milwaukee, Wisconsin). The standard parasternal and apical views with the highest possible quality were carefully selected and digitally stored for off-line analysis. The LV EDV and ESV were obtained to calculate LV EF by using the Simpson’s method from apical four- and two-chamber views (23). The MR volume was calculated as the difference of mitral annulus area (MAA) and the mitral time velocity integral during diastole, and aortic stroke volume was calculated by multiplying the LV outflow tract area and time velocity integral at systole. The MR fraction was then calculated as MR volume divided by mitral stroke volume.

The MAA was estimated by the product of annulus diameters in apical four- and two-chamber views (14,21). The tenting area (TA) of the mitral valve was measured by tracing between the atrial surface of the leaflets and the mitral annular plane from the apical four-chamber view (Fig. 1). The proximal flow convergence (PFC) area of MR was obtained from the apical views in color Doppler flow image with the Doppler color gain carefully adjusted to maximize signal without random noise velocities (3,12–14,20). The setting of the color Doppler flow image was consistent before and after CRT. The maximal radius (r) of the PFC area was measured after a baseline shift of the color flow to decrease the aliasing velocity (V). The MR flow rate was then calculated as $2 \times \pi \times r^2 \times V$. A dynamic change in the degree of MR was evaluated by frame-by-frame analysis throughout the regurgitation period, and then images at the timing of the maximum PFC area at early- and late-systole, and minimum at mid-systole were separately selected for assessing the phasic change and to calculate early/late peaks ratio in MAA, TA, and MR flow rate (Fig. 2).

Statistical analysis. Values were expressed as mean ± SD. Comparison of echocardiographic parameters between before and after CRT were made with the paired $t$ test. Repeated measures analysis of variance was used to compare among three cardiac phases (early-, mid-, and late-systole). When differences were found, any two phases were compared using Student $t$ test with Bonferroni correction. One-way analysis of variance followed by post hoc with Bonferroni test was used to compare among three subgroups defined according to the etiology of underlying LV disease (idiopathic dilated cardiomyopathy, or myocardial infarction with or without inferoposterior wall). Linear regression was used for correlation of variables of interest. Multivariate linear regression analysis was performed to identify determinant factors of MR early/late flow ratio, and the significant variables on univariate analysis were entered into models. Differences were considered significant at $p < 0.05$. 

Figure 1. Schema explaining echocardiographic measurements of mitral annulus (arrow) and tenting area (oblique line) in apical four-chamber view. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.
Inter-observer and intra-observer variabilities for measurement of MAA, TA, and the radius of MR flow area by the PFC method were obtained by analysis of 10 random images by two independent blinded observers and by the same observer at two different time points. The results were analyzed by both least squares fit linear regression analysis and the Bland-Altman method (25).

RESULTS

Dynamic changes of functional MR and mitral valve deformations. A phasic pattern with two peaks at early- and late-systole and decrease in mid-systole was noticed in 57 of 60 patients (95%) (Fig. 2). Second peak was observed at late-systole (n = 37) or isovolumic relaxation time (n = 20). In the remaining three patients (5%), a peak during late-systole or isovolumic relaxation time was not observed, and therefore a late-systolic image was defined as image at end-systole from electrocardiogram. In these three patients, the etiology of LV disease was idiopathic dilated cardiomyopathy in one and inferoposterior infarction in two. The QRS duration was 138, 144, and 222 ms, respectively.

In these 60 patients, MR volume and fraction were 54.8 ± 22.3 ml and 51.3 ± 10.9%, respectively. There were significant differences in MAA, TA, and MR flow rate among three cardiac phases (all p < 0.001) (Fig. 3). The MAA and TA at early-systole were significantly larger than those at late-systole (7.23 ± 1.43 cm² vs. 6.23 ± 1.26 cm² for MAA, and 1.49 ± 0.64 cm² vs. 1.20 ± 0.52 cm² for TA, both p < 0.01) (Fig. 3). Early-systolic peak of MR flow rate was much larger than late-systolic peak (128.4 ± 64.3 ml/s vs. 73.9 ± 55.1 ml/s, p < 0.001) with a mean value of MR flow early/late peaks ratio of 2.50 ± 1.99 (Fig. 3). Peak MR flow rate was significantly correlated with corresponding MAA and TA in these 60 patients (Table 1).

Relationship of MR dynamics with clinical and echocardiographic findings. By the univariate analysis, QRS duration (r = 0.55, p < 0.001), EDV (r = 0.26, p = 0.048), and TA ratio (r = 0.31, p = 0.02) were significantly correlated with MR flow early/late peaks ratio, whereas age (p = 0.9), ESV (p = 0.06), EF (p = 0.5), MR volume (p = 0.4) and fraction (p = 0.6), and MAA ratio (p = 0.6) did not correlate (Table 2 and Fig. 4). There were no significant differences in MR flow ratio among the patients.

Figure 2. Example images of instantaneous proximal flow convergence region (arrows) during regurgitation period with color Doppler imaging (upper). Typical pattern of mitral regurgitation (MR) flow rate showing an increase to maximum size at early-systole, a decrease at mid-systole, and a re-increase at late-systole or isovolumetric relaxation period (lower).

Figure 3. Summary of mitral annulus area (A), tenting area (B), and mitral regurgitation (MR) flow rate (C). Note decrease of these parameters during mid-systole, followed by an increase during late-systole. These parameters at early-systolic peak were larger than those at late-systolic peak.
with idiopathic dilated cardiomyopathy (2.97 ± 2.77), infarction with (1.87 ± 1.41) or without (2.73 ± 1.61) inferoposterior wall (p = 0.2). When all significant parameters by univariate analysis were included in the multivariate regression analysis (QRS duration, EDV, and TA ratio), QRS duration (p < 0.001) and TA ratio (p = 0.04) were independent factors for MR flow ratio (Table 2). The partial correlations were 0.48 for QRS duration and 0.29 for TA ratio.

Both early- and late-systolic peak MR flow rates were significantly correlated with MR volume (r = 0.67, p < 0.001 and r = 0.42, p = 0.001) and fraction (r = 0.63, p < 0.001 and r = 0.43, p = 0.007), respectively. However, there were no significant correlations of MR volume (p = 0.4) and fraction (p = 0.6) with the early/late flow ratio of these two peaks.

The effect of CRT on dynamics of functional MR. In 19 patients with CRT, EDV (358.7 ± 82.5 ml to 328.3 ± 96.9 ml, p = 0.01) and ESV (274.8 ± 74.1 ml to 248.8 ± 92.0 ml, p = 0.03) were significantly reduced after CRT, whereas EF did not change (23.7 ± 7.8% to 25.3 ± 9.2%, p = 0.4).

Table 3 shows the results for the measurement of MAA and TA in early-, mid-, and late-systolic phases before and after CRT. There were no significant differences in MAA between before and after CRT in any phase. In contrast, early-systolic TA significantly diminished after CRT, whereas mid- and late-systolic parameter were unchanged.

The CRT induced 27.0 ± 33.3% reduction in MR volume from 61.6 ± 19.8 ml to 41.2 ± 14.1 ml (p = 0.002).

### Table 2. The Relationships of MR Flow Ratio With Clinical and Echocardiographic Findings

<table>
<thead>
<tr>
<th></th>
<th>MAA</th>
<th>TA</th>
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<tbody>
<tr>
<td></td>
<td>r Value</td>
<td>p Value</td>
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<tr>
<td>Overall (n = 60)</td>
<td></td>
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<tr>
<td>Early-systolic flow</td>
<td>0.36</td>
<td>0.006</td>
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<tr>
<td>Late-systolic flow</td>
<td>0.39</td>
<td>0.002</td>
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<tr>
<td>After CRT (n = 19)</td>
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<td></td>
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<tr>
<td>Early-systolic flow</td>
<td>0.22</td>
<td>0.4</td>
</tr>
<tr>
<td>Late-systolic flow</td>
<td>0.19</td>
<td>0.5</td>
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</table>

EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; MAA = mitral annulus area; MR = mitral regurgitation; TA = tenting area.

The MR fraction also decreased from 51.6 ± 8.3% to 39.8 ± 13.1% (p = 0.002) with 21.6 ± 26.1% reduction. Comparing instantaneous regurgitation flow among at early-, mid-, and late-systolic phases, flow rate decreased at early-systolic, whereas it did not change at mid- and late-systole (Table 3). Therefore, changes of late-systolic flow rate (−0.7 ± 65.2%) significantly underestimated those of MR volume (p = 0.03) and fraction (p = 0.046). Changes after CRT in MR volume (p = 0.5) and fraction (p = 0.1) did not significantly differ from that in early-systolic peak flow (34.3 ± 35.9%). Figure 5 illustrates typical examples of color Doppler images before and after CRT. The MR flow rate significantly related to corresponding TA after CRT, whereas no correlation was observed between MR flow rate and MAA (Table 1).

### Observer variability. Correlations for inter-observer and intra-observer variability of echocardiographic measurements were r = 0.88 and r = 0.86 for MAA, r = 0.87 and r = 0.86 for TA, and r = 0.80 and r = 0.82 for the radius of MR PFC area, respectively. From the Bland-Altman method, inter-observer and intra-observer variabilities were 0.84 cm² and 0.66 cm² for MAA, 0.29 cm² and 0.16 cm² for TA, respectively.

### Table 3. The Effect of CRT on Mitral Valve Deformations and MR Flow Rate

<table>
<thead>
<tr>
<th></th>
<th>Before CRT</th>
<th>After CRT</th>
<th>p Value</th>
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<tbody>
<tr>
<td>MAA (cm²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early-systole</td>
<td>6.13 ± 0.98</td>
<td>5.82 ± 1.23</td>
<td>0.3</td>
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<tr>
<td>Mid-systole</td>
<td>5.06 ± 1.48</td>
<td>5.15 ± 1.36</td>
<td>0.8</td>
</tr>
<tr>
<td>Late-systole</td>
<td>5.87 ± 1.09</td>
<td>5.67 ± 1.49</td>
<td>0.5</td>
</tr>
<tr>
<td>Early/late ratio</td>
<td>1.05 ± 0.09</td>
<td>1.04 ± 0.09</td>
<td>0.7</td>
</tr>
<tr>
<td>TA (cm²)</td>
<td></td>
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<tr>
<td>Early-systole</td>
<td>1.53 ± 0.54</td>
<td>1.14 ± 0.62</td>
<td>0.003</td>
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<tr>
<td>Mid-systole</td>
<td>0.94 ± 0.39</td>
<td>0.75 ± 0.47</td>
<td>0.07</td>
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<tr>
<td>Late-systole</td>
<td>1.23 ± 0.48</td>
<td>1.06 ± 0.56</td>
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<tr>
<td>Early/late ratio</td>
<td>1.28 ± 0.26</td>
<td>1.09 ± 0.24</td>
<td>0.03</td>
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<tr>
<td>MR flow rate (ml/s)</td>
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<tr>
<td>Early-systole</td>
<td>143.9 ± 60.8</td>
<td>90.7 ± 54.1</td>
<td>0.003</td>
</tr>
<tr>
<td>Mid-systole</td>
<td>12.7 ± 12.2</td>
<td>11.2 ± 25.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Late-systole</td>
<td>61.5 ± 55.0</td>
<td>51.2 ± 40.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Early/late ratio</td>
<td>3.35 ± 2.34</td>
<td>2.26 ± 1.46</td>
<td>0.04</td>
</tr>
</tbody>
</table>

CRT = cardiac resynchronization therapy; MAA = mitral annulus area; MR = mitral regurgitation; TA = tenting area.
TA, and 0.07 cm and 0.07 cm for the radius of MR PFC area, respectively.

**DISCUSSION**

The present study demonstrated that dynamic changes of regurgitation flow during a cardiac cycle were associated with QRS duration in patients with functional MR. The phasic pattern of MR changed after CRT as a result of the reduction of regurgitation flow in early-systole. Similar changes were observed in tethering of the leaflet rather than annulus size.

**Phasic changes of MR flow and valve deformations.** Instantaneous regurgitation flow rate of MR was not fixed during the regurgitation period, which varied in response to ventricular volume and shape, load conditions, and etiology of mitral valve lesions (10–14). In patients with rheumatic valve disease, the flow rate was constant, but it was increased from mid- to late-systole in patients with mitral valve prolapse (12).

In functional MR from dilated and remodeling LV, mitral annular enlargement, tethering of the leaflet owing to displaced papillary muscle, and transmitral pressure were thought to determine the severity of regurgitation flow (5–9). These geometric and hemodynamic factors changed throughout a cardiac cycle, leading to unique phasic variation of functional MR (12–14). Schwammenthal et al. (12), who had measured the temporal change in regurgitation flow with the PFC method, found a biphasic pattern with early- and late-systolic peaks in patients with functional MR. This initial observation has been experimentally confirmed by Shiota et al. (13) using electromagnetic flowmeters and the PFC method. Hung et al. (14) had shown that transmitral pressure opposing tethering of the leaflet made a stronger contribution than annulus area for dynamics of functional MR.

The mitral deformations (tethering of the leaflet and annulus dilation) also showed phasic pattern during a cardiac cycle. Yiu et al. (8) demonstrated that mitral valve tenting by tethering of the leaflet, which was determined by displaced papillary muscles and by regional wall motion abnormality of segments assisting papillary muscles, was the most powerful predictor for the severity of functional MR. In their study, early-systolic TA, which was larger than late systolic TA, showed better correlation with the severity of MR. On the other hand, Kaplan et al. reported that MAA in patients with functional MR decreased from early- to late-systole and increased in the latter half of systole (26). They suggested that the three-dimensional geometry of MAA might be different between early- and late-systole. Therefore, mitral valve deformations might have different effects on MR during these two systolic phases. Actually, we noticed that changes of tethering of the leaflet and regurgitation flow rate after CRT were different between early- and late-systole, indicating the differences of determinant factors between these two peaks. However, the mechanisms of the phasic pattern of functional MR remained unknown.

**Effect of CRT on functional MR.** Recent studies showed acute beneficial effects of CRT in patients with functional MR (20,21). Breithardt et al. (20) had reported that an increase of transmitral pressure, generating closing force to the leaflet, was an important factor for reduction of MR in the first week after CRT. They found that an increase in transmitral pressure provided decreased tethering of the leaflet. Kanzaki et al., who measured regional mechanical synchrony by echocardiographic strain imaging technique, demonstrated that re-coordinated synchrony between papillary muscle insertion segments by CRT related to the reduction of MR, whereas mitral annulus size was not changed after CRT (21). In the present study, CRT provided approximately a 25% reduction of functional MR >3 months after pacemaker implantation. The TA decreased at early-systole, although MAA did not change during any phases. As a consequence, in both short-term and mid-term follow-up periods, reduction of MR after

![Figure 5](https://example.com/figure5.jpg)

Figure 5. Examples of color Doppler images before and after cardiac resynchronization therapy (CRT). Before CRT, the proximal flow convergence region of early-systolic peak was much larger than that of late-systolic peak (A). After CRT, the opposite pattern was observed (B).
CRT might be caused by alternation of tethering of the leaflet rather than annulus dilation. Uncoordinated regional LV activation in the segments attaching papillary muscles might prevent the optimal timing and position for coaptation of mitral valve leaflets (20,21). Additionally, we demonstrated that regurgitation flow decreased after CRT only in early-systole, not in late-systolic peak, suggesting that early-systolic regurgitation flow might be caused by severe ventricular asynchrony. The CRT might re-coordinate regional LV activation, leading to reduction of early-systolic MR.

**Study limitations.** Several limitations of our study should be mentioned. First, the number of patients was small (n = 60), and CRT was performed only in 19 patients (32%) with relatively wide QRS duration (161.6 ± 33.3 ms). Non-selected and randomized studies are necessary to test the effect of CRT on the phasic pattern of MR in patients with narrow QRS duration. Additionally, 2 of 60 patients had pacemaker-induced rhythm, although the mechanical ventricular asynchrony induced by pacing might be different from the remaining patients.

Second, mitral valve deformations and PFC areas were estimated by two-dimensional echocardiography. The imaging planes of two-dimensional echocardiography during systole may not have been fixed at the same location of the mitral valve orifice, although we carefully selected stable images during image acquisition. Three-dimensional echocardiography allows us to assess these parameters more accurately without elliptic (27) or hemispheric assumptions (28). In addition, PFC area of regurgitation flow was measured by color two-dimensional Doppler imaging with a mean frame rate of 22.4 ± 7.2 Hz when the images were expanded by using regional expansion selection mode. Color M-mode imaging could provide higher temporal resolution. However, its cursor direction might not be placed parallel to the axis of PFC area.

Third, observer variability of echocardiography was based on the measurement only. Reproducibility of image acquisition was not examined. Additionally, observer variability of PFC area of MR was relatively low, and might have affected the results in this study. However, because most patients showed similar results on dynamic changes of MR flow, our essential message on this matter would hold true.

Finally, the duration of the QRS complex from the 12-lead surface electrocardiogram might not be an optimal marker to address ventricular asynchrony, although it was used to select candidates for CRT in the previous studies (15,16,18–21). The electrical conduction disturbance and mechanical ventricular asynchrony might be different, although there was a close relationship. Recently introduced echocardiographic techniques, such as tissue Doppler imaging and strain-rate imaging, have a potential for more accurate assessment of global and regional ventricular systolic asynchrony (29,30). Further studies may be needed to confirm our results by using these techniques.

**Conclusions.** Biphasic pattern was found in functional MR, and the ratio of flow rate at two peaks correlated with QRS duration. The CRT decreased regurgitation flow volume by reducing early-systolic MR but not late-systolic MR, resulting in the change in phasic pattern of functional MR.

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