Medicine, Osaka, Japan; and the Department of Cardiovascular Surgery (K.T.), Japan Labor Health and Welfare Organization Osaka Rosai Hospital, Sakai, Japan.

Methods and Results—Twenty-four patients with dilated cardiomyopathy underwent 64-row MDCT before and 2 months after RMA. All patients underwent stringent downsizing annuloplasty with a semirigid complete ring. Reconstructed images were used to calculate LV end-diastolic index (EDVI) and end-systolic volume index (ESVI), LV ejection fraction, and regional and global end-systolic wall stress (ESS). After RMA, LVEDVI and LVESVI decreased from 151±52 to 131±53 mL/m² (P=0.0001) and from 114±48 to 92±50 mL/m² (P=0.0001), respectively. Global ESS decreased from 157±43 to 139±50 kdyne/cm² (P=0.01), and LV ejection fraction improved from 27±8.0 to 33±13% (P=0.0007). There were significant correlations between change in LVEDVI and LVESVI (r=0.88, P<0.0001) and change in LVESVI and global ESS (r=0.68, P=0.0002). Moreover, the magnitude of increase in LV ejection fraction significantly correlated with the degree of reduction in global ESS (r=−0.61, P=0.002). Patients without significant reverse LV remodeling had significantly higher preoperative and postoperative global ESS than those with it.

Conclusions—Our study suggests that decrease in afterload after reduction in volume overload was responsible for postoperative reverse LV remodeling process after RMA. (Circulation. 2010;122[suppl 1]:S3–S9.)

Key Words: mitral valve • cardiomyopathy • annuloplasty • wall stress

Functional mitral regurgitation (MR) is a common complication in both ischemic and nonischemic dilated cardiomyopathy and leads to an increased left ventricular (LV) volume overload. This condition further aggravates LV remodeling process, eventually leading to congestive heart failure. To resolve this vicious cycle, Bolling et al first reported the feasibility of undersized mitral annuloplasty in patients with end-stage cardiomyopathy. They observed reverse LV remodeling (decrease in LV volumes and increase in ejection fraction) after correction of MR in such failing ventricle, although further decline in LV ejection performance was to be expected as a result of increase in afterload (systolic myocardial wall stress) accompanied by the abolition of the low-impedance pathway for ejection into the left atrium. Thereafter, several studies demonstrated that undersized mitral annuloplasty or restrictive mitral annuloplasty (RMA) procedure could induce reverse LV remodeling.

However, to date, the mechanism how RMA can lead to reverse LV remodeling process remains unclear. In the present study, we hypothesized that change in systolic myocardial wall stress may be a key explaining of reverse LV remodeling after correction of functional MR in dilated cardiomyopathy. We recently developed a software package to determine local myocardial stress using cineangiographic 64-row multidetector computed tomographic (cine-MDCT) images. To test our hypothesis, therefore, we used both cine-MDCT images and our developed software.

Methods

Patients

The study group consisted of 24 patients (19 men and 5 women, mean age of 64±9.4) who underwent 64-row MDCT before and after RMA between January 2007 and December 2008. All patients had a diagnosis of advanced dilated cardiomyopathy with LV dysfunction (LV ejection fraction <40%) and congestive heart failure symptoms despite the maximal medical treatment. All patients had 3 to 4+ functional MR secondary to LV and annular dilatation and systolic restrictive motion of mitral leaflets on echo.
Table 1. Preoperative Patient Characteristics*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64±9.4</td>
</tr>
<tr>
<td>Sex, male</td>
<td>19</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>6 (25)</td>
</tr>
<tr>
<td>III</td>
<td>15 (62.5)</td>
</tr>
<tr>
<td>IV</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>Mitral regurgitation grade</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>11 (46)</td>
</tr>
<tr>
<td>Moderate</td>
<td>20 (83)</td>
</tr>
<tr>
<td>Diuretics use, n (%)</td>
<td>18 (75)</td>
</tr>
</tbody>
</table>

*ACE indicates angiotensin-converting enzyme; and ARB, angiotensin receptor blocker.

Cardiography. Eleven patients also had coronary artery disease and were classified as having ischemic dilated cardiomyopathy. The study protocol was approved by the institutional review board, and all patients provided informed consent. Table 1 shows preoperative clinical profile of all patients.

Surgical Techniques

All operation was performed with conventional cardiopulmonary bypass with mild hypothermia. Myocardial protection was achieved by both antegrade and retrograde cold blood cardioplegia. All patients underwent a stringent RMA with the implantation of semirigid complete ring (Carpentier Edwards Physio Ring; Edward Lifesciences, Irvine, Calif). The size of annuloplasty ring used was 24 mm in 12 (50%), 26 mm in 11 (46%), and 28 mm in 1 (4%). Simultaneous procedure included coronary artery bypass grafting in 11 (46%) and tricuspid annuloplasty in 15 (63%).

MDCT Image Acquisition

Image acquisition was performed 1 month before surgery and repeated at 2.3 months after surgery. During each image acquisition, upper extremity blood pressure in substitution for invasive measurement of LV end-systolic pressure was recorded with an automated digital cuff. After an initial scout image and a timing bolus scan, a volume data set of the whole heart (collimation, 64/0.625 mm; gantry rotation time, 350 ms; mean scanning time, approximately 5 seconds) was acquired with retrospective electrocardiographic gating. For enhancement of LV cavity, 0.8 mL/kg of nonionic contrast medium was administered at a flow rate of 4 mL/s. Ten data sets were obtained at 10% R-R interval increments throughout the cardiac cycle (5% to 95%). A stack of consecutive images (each of 8 mm thick and a gap of 2 mm) was reconstructed in the short-axis of LV. To calculate local end-systolic wall stress (ESS), LV horizontal and vertical long-axis cine-images according to standardized LV segmentation were reconstructed throughout one cardiac cycle and stored as audio video interleave files using commercially available software (Aquarius Net Station, TeraRecon, Inc, San Mateo, Calif). Image acquisitions were successful without any complications in all patients. All image processing were performed by a well-experienced radiologist (S.H.).

Echocardiography

All patients were assessed by 2-dimensional echocardiography around the same time as MDCT study. Degree of mitral regurgitation was quantified by means of echocardiographic Doppler analysis using a 5-point scale (from 0 to 4+).

Statistical Analysis

The SPSS (version 11.0, SPSS Inc) software was used for statistical analysis. The continuous variables are presented as mean±SD and compared using paired and unpaired t test. Categorical variables were compared by χ² analysis and Fisher exact test. Correlation

**Figure 1.** Representative vertical and horizontal LV end-systolic images to calculate the regional ESS. LV endocardial and epicardial borders were traced. Our software automatically calculated regional ESS along 100 chords evenly spaced along the epicardial border in each image. For analysis, the LV cavity was divided into totally 12 regions by long axis and perpendicular short axes at equal intervals. See text for details.
Surgical and Late Clinical Results
All patients well tolerated the operation. On echocardiography, the degree of MR was less than grade 2+ in all patients after surgery and significantly decreased from 3.3±0.6 to 0.3±0.5 (P<0.0001). During a mean follow-up of 18 months, 5 patients (21%) had recurrent congestive heart failure symptoms in NYHA (New York Heart Association) class III or IV. The other patients were well in NYHA class I or II.

Changes in LV Ejection Performance and Wall Stress Before and After RMA
Heart rate and blood pressure at the time of image acquisition did not significantly change postoperatively (Table 2). LVEDVI significantly decreased with an average reduction of 20 mL/m² (13% reduction) and LVESVI also decreased with an average reduction of 21 mL/m² (21% reduction) (Table 3). Mean LVEF significantly improved from 27% to 33% after surgery. The measured value of postoperative LVEF was higher than the predictive value (28%) when we assumed that stroke volume did not change after surgery. Reduction percentage in LVEDVI and LVESVI and increase in LVEF were larger in patients with ischemic etiology compared with those with nonischemic etiology; ΔLVEDVI

\[ \text{ΔLVEDVI} = \text{LVEDVI}_{\text{pre}} - \text{LVEDVI}_{\text{post}} \]

Table 3. Changes in LV Function, Geometry, and Wall Stress on MDCT Study

<table>
<thead>
<tr>
<th>Variables</th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>Mean Percentage Change</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDVI, mL/m²</td>
<td>151±52</td>
<td>131±53</td>
<td>−13%</td>
<td>0.0001</td>
</tr>
<tr>
<td>LVESVI, mL/m²</td>
<td>113±48</td>
<td>92±50</td>
<td>−21%</td>
<td>0.0001</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>27±8.0</td>
<td>33±13</td>
<td>6.9%</td>
<td>0.0007</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>121±39</td>
<td>112±32</td>
<td>−3.7%</td>
<td>0.13</td>
</tr>
<tr>
<td>Sphericity index, diastole</td>
<td>0.71±0.02</td>
<td>0.68±0.02</td>
<td>−3.8%</td>
<td>0.01</td>
</tr>
<tr>
<td>Sphericity index, systole</td>
<td>0.69±0.09</td>
<td>0.66±0.10</td>
<td>−4.1%</td>
<td>0.02</td>
</tr>
<tr>
<td>Global ESS, kdyne/cm²</td>
<td>157±43</td>
<td>139±50</td>
<td>−11%</td>
<td>0.01</td>
</tr>
<tr>
<td>Basal average ESS, kdyne/cm²</td>
<td>162±44</td>
<td>147±53</td>
<td>−9.3%</td>
<td>0.03</td>
</tr>
<tr>
<td>Mid average ESS, kdyne/cm²</td>
<td>164±45</td>
<td>142±51</td>
<td>−13%</td>
<td>0.004</td>
</tr>
<tr>
<td>Apical average ESS, kdyne/cm²</td>
<td>145±43</td>
<td>132±49</td>
<td>−9.5%</td>
<td>0.05</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; and DBP, diastolic blood pressure.

Results

Impact of ESS Reduction on Postoperative Clinical Outcomes
When significant reverse remodeling was defined as a volume reduction exceeding 15% in LVESVI, 17 patients (71%) showed significant reverse remodeling and 7 (2 in ischemic and 5 in nonischemic) showed no or poor reverse remodeling 2 months after RMA. Patients without significant reverse remodeling had higher preoperative global ESS (186±20 versus 143±44 kdyne/cm², P=0.01) and persis-

Figure 2. Individual change of ESS/ESVI value before and after RMA. (*) between preoperative mean value and postoperative value.

(-16% versus −9.4%, P=0.27), ΔLVESVI (−27% versus −13%, P=0.16), and ΔLVEF (+9.6% versus +3.2%, P=0.07); however, those differences did not reach statistical significance as of 2-month follow-up.

LV mass index did not significantly change. Both end-diastolic and end-systolic sphericity indices significantly decreased after the operation. The ratio of global ESS to LVESVI (ESS/ESVI), which was a relatively load-independent index for estimating myocardial contractility, significantly improved from 1.5±0.5 to 1.7±0.5 (P=0.008), with a mean increase of 17% (Figure 2).

Change in LV Global and Regional Wall Stress After RMA
Change in regional ESS at 12 segments was shown in Figure 3. Regional ESS was generally reduced at all segments, especially at anterior and inferior segments. Consequently, global ESS significantly decreased with a mean reduction of 11% (Table 3). Postoperative reduction in average ESS was larger in midventricular level (13% reduction) than in basal and apical ventricular level (9% reduction for each).

Relationship Between LV Volume, Wall Stress, and Ejection Performance
There was a strong positive correlation (r=0.88, P<0.0001) between ΔLVEDVI and ΔLVESVI (Figure 4A). ΔLVESVI was significantly related to Δglobal ESS (r=0.68, P=0.0002) (Figure 4B). ΔGlobal ESS significantly correlated with ΔLVEF (r=−0.61, P=0.002) (Figure 4C). Moreover, weak correlation was noted between ΔESS/ESVI and ΔLVEF (r=0.48, P=0.02), ΔEnd-systolic sphericity index weakly but significantly correlated with Δglobal ESS (r=0.46, P=0.02).

Table 2. Preoperative and Postoperative Heart Rate and Blood Pressure at the Time of MDCT Study

<table>
<thead>
<tr>
<th>Variables</th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>70±10</td>
<td>72±11</td>
<td>0.26</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>111±16</td>
<td>106±14</td>
<td>0.09</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>64±13</td>
<td>62±12</td>
<td>0.76</td>
</tr>
<tr>
<td>LV end-diastolic pressure</td>
<td>89±13</td>
<td>87±11</td>
<td>0.36</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; and DBP, diastolic blood pressure.

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tently higher postoperative global ESS (190±35 versus 119±41 kdyne/cm², \(P = 0.0004\)) than those with it (Figure 5), whereas preoperative degree of LV remodeling was similar between groups (LVESVI; 127±40 versus 107±51 mL/m², \(P = 0.34\)). Four of 7 patients (57%) without significant reverse LV remodeling developed late recurrent heart failure, compared with 1 of 17 patients (5.9%) with it \((P = 0.02)\).

**Discussion**

Major findings of this study were (1) ESS significantly decreased after RMA, and the reduction in ESS was strongly associated with the improvement in LVEF; and (2) ESS/ESVI significantly improved, and the improvement in ESS/ESVI was weakly but significantly correlated with the improvement in LVEF. These findings indicate that the improvement in LV ejection performance was mostly related to the afterload reduction rather than to the improvement of LV contractility as of 2 months after the operation. That is, the mechanism of reverse LV remodeling process is related to the afterload reduction derived from ventricular volume unloading by eliminating MR.

It was once believed that the presence of chronic MR creates a systolic unloading effect by providing a low-resistance ejection into the left atrium. This traditional hypothesis held that the mitral valve functions as a “pop off valve” for the failing ventricle and surgical correction might have prohibitive risks in patients with severely remodeled LV because of postoperative afterload excess and subsequent...
decline in LV ejection performance. However, several recent studies have shown an acceptably low operative mortality and have suggested that RMA can lead to reverse LV remodeling. Consequently, it has been postulated that RMA could reduce myocardial wall stress and promote reverse LV remodeling; however, change in regional myocardial stress after RMA has not been fully investigated. To our knowledge, this is the first study to assess the changes in systolic wall stress before and after RMA in patients with cardiomyopathy using cine-MDCT images.

Our software demonstrated that regional ESS largely decreased after RMA, leading to global ESS reduction. Few studies have examined the change in wall stress after valve repair in patients with advanced cardiomyopathy. A previous experimental report demonstrated that annular reduction could reduce regional ESS by reducing radii of curvatures at basal, equatorial, and even the apical levels without any reduction in LV volume. These data appeared to support Bolling’s concept that undersizing the annulus acutely reduces ventricular volume reduction and thereby decreased LV wall stress. However, in the present study, reduction in ESS was mostly related to LV volume reduction. Both stronger correlation between ΔLVESVI and Δglobal ESS (r = 0.68) compared with that between Δsphericity index and Δglobal ESS (r = 0.46) and lesser ESS reduction in basal LV (9%) compared with that in mid LV (13%) might suggest that the effect of volume unloading had a much greater impact on ESS reduction than the direct reshaping effect. Therefore, LV unloading and subsequent reduction in wall stress would lead to reversal of ventricular remodeling and favorable change in LV shape. The issue about the relative impact of direct annular remodeling on change in ESS requires further investigation.

There is accumulating evidence that reverse LV remodeling has been demonstrated as a result of either annuloplasty alone or in combination with coronary artery bypass grafting. Bolling et al observed 8% reduction in EDV and 15% reduction in ESV with the improvement in LVEF from 0.18 to 0.27 at 6 months after the operation. Subsequently, they also reported 23% reduction in EDV and 28% reduction in ESV with the change in LVEF, from 0.20 to 0.26 at a later period. Acker et al also reported that significant reverse LV remodeling persisted up to 18 months after mitral valve surgery in patients with nonischemic heart failure. These findings suggest that reverse LV remodeling is a gradual and time-dependent process. Many other echocardiographic studies also have reported that significant decrease in LV dimensions and increase in LVEF (“reverse remodeling”) in most of patients. Our data were largely consistent with those of previous reports; 71% of patients showed significant reverse remodeling at 2-month postoperative MDCT study. However, persistent or progressive remodeling pattern is also documented despite an initially successful mitral repair with longer follow-up. De Bonis et al reported that of 111 patients with advanced cardiomyopathy who underwent RMA, 52% of their patients showed reverse LV remodeling, whereas 48% showed unchanged or progressive remodeling at 2-year follow-up. Gelsomino et al observed significant reverse LV remodeling in 44% of 251 patients undergoing RMA for ischemic MR and continued or progressive LV remodeling in 56% at 5 years after the operation. These conflicting results are likely to be attributed to the complex mechanisms of functional MR itself, which include not only annular dilatation but also papillary muscle displacement and chordal tethering caused by LV remodeling. Although RMA could improve mitral leaflet coaptation, most recent studies demonstrated that simple annuloplasty repair could not necessarily improve leaflet tethering enough to avoid recurrent MR and therefore yielded the absence of reverse LV remodeling. Current results demonstrated that the resolution of annular problem by RMA could provide, at least, less of a stimulus for ongoing pathological myocardial remodeling process but could not restore normal LV function and configuration as seen in the nonfailing hearts. The complex mechanism involving the valvular and subvalvular apparatus might require more comprehensive reparative correction rather than simple annular repair to improve the results.

Our result demonstrated that reverse LV remodeling process after RMA was induced by reduction of not only volume overload (ventricular preload) but also regional and global systolic wall stress (afterload). Change in ejection performance after RMA results from a complex interaction of contractile function, ventricular preload, and afterload. Reduced ventricular preload indicated by the reduction in EDV (eliminating MR) would have actually tended to reduce ejection performance. However, our data indicated that reduced ventricular preload also allowed reduced systolic chamber size and elliptical LV shape, which resulted in reduction of the radius term in the wall stress equation, allowing systolic wall stress to be reduced. Reduced afterload allowed further reduction in ESV, overcoming the fall in EDV to allow ejection performance to improve. Furthermore, our result demonstrated modest increase in ESS/ESVI, suggesting that the potential benefits of RMA might extend to an improvement in myocardial contractility. The relationship between ΔLVEF and ΔESS/ESVI indicated that myocardial contractile recovery might contribute a favorable effect to reverse remodeling process. However, the implication of this improvement should not be overestimated. Carabello et al...
reported that an ESS/ESVI of <2.6 indicated a poor prognosis in patients with MR. Therefore, this positive effect might not be clinically relevant because postoperative mean ESS/ESVI of 1.7 remained extremely low in our cohort. Indeed, some previous studies demonstrated that the role of valve repair for the failing hearts was limited in terms of survival benefits. Enríquez-Sarano et al\(^2\) showed the ongoing poor effects of mitral repair on 15-year survival in patients with ischemic MR. Braun et al\(^5\) reported the limited effect of RMA in patients with LV end-diastolic dimension >65 mm. These results imply that beneficial effects of RMA on LV performance might not be enough to overcome the intrinsic LV failure. To date, there has been no conclusive data about the true effect of mitral valve surgery on the prognosis. Although 2 large series concluded no clear survival benefit of annuloplasty repair for functional MR compared with medical therapy or isolated coronary bypass grafting,\(^22,23\) those were limited because of retrospective study design. It is hoped that randomized, prospective trials will resolve this problem.

Our result partly explains the failure of reverse remodeling process in terms of measured LV wall stress using our software. Grossman et al\(^24\) hypothesized that compensatory mechanism to maintain physiological myocardial wall stress (afterload) could be mediated through the addition of new sarcomeres and the development of eccentric myocardial hypertrophy in chronic volume-overload LV. However, inability to sustain addition of new sarcomeres in progressive volume overload could result in high myocardial wall stress, leading to decreased myocardial fiber shortening and ventricular failure (decompensated MR). Our data suggest that RMA could partly attenuate this pathological myocardial process even in the decompensated MR. However, the fact that patients with preoperative high global ESS showed persistence of the high ESS, which was probably a major factor behind the reduced postoperative ejection performance and, therefore, the adverse clinical outcomes, implied the onset of irreversible pathological process of myocardial dysfunction.\(^25\)

Wall stress is a major determinant of LV architecture, function, and myocardial composition. Therefore, further analyses using our software might become helpful to assess the reverse LV remodeling viability in patients with decompensated MR.

Limitations

There are several limitations in this study. The patient cohort is small and relatively heterogeneous. Moreover, various surgical procedures added and type of annuloplasty ring used may influence the outcomes. In our series, change in LVESVI and LVEF was not significantly different between ischemic and nonischemic group as of 2 months after the operation. Moreover, we have reported that revascularization alone could not always decrease regional stress in patients with LV dysfunction.\(^26\) Therefore, we think that the effect of revascularization could be minimized in our results. However, those differences might become obvious with further follow-up, because the effect of revascularization can be considerably delayed over 3 months in the failing ventricle.\(^27\) We preferably used semirigid complete annuloplasty ring. Previous report suggested that the type of annuloplasty ring could influence the postoperative LV function\(^28\); therefore, our results would not be applicable to patients who received another type of prosthesis.

We estimated local ESS using the simplified formula derived by Janz\(^9\) because this method is easy to apply when clinically determining local ESS. Although the methodological problems have been discussed in previous reports,\(^9,28\) it is considered that values obtained by the Janz method are comparable to those obtained by the finite element method within an error of ≤10%.

Finally, we used a 64-row MDCT as the image modality. As found in other conventional modalities, there are inherent limitations, including the need for contrast medium and radiation exposure. However, to estimate local wall stress, its high spatial resolution enables us to precisely estimate regional wall thickness and appropriately compare preoperative values with postoperative values. Moreover, because of current increasing use of cardiac defibrillator or biventricular pacemaker in patients with heart failure, we think that MDCT is useful to noninvasively assess accurate ventricular function.\(^29,30\)

Conclusion

In conclusion, RMA could reduce regional and global wall stress by eliminating ventricular preload. Our study suggested that the extent of reduction in afterload was partly responsible for postoperative reverse LV remodeling process after RMA.

Disclosures

None.

References


Mechanism of Beneficial Effects of Restrictive Mitral Annuloplasty in Patients With Dilated Cardiomyopathy and Functional Mitral Regurgitation
Koji Takeda, Kazuhiro Taniguchi, Yasuhiro Shudo, Satoshi Kainuma, Seiki Hamada, Hajime Matsue, Goro Matsumiya and Yoshiki Sawa

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