Magnetic Resonance Imaging With 3-Dimensional Analysis of Left Ventricular Remodeling in Isolated Mitral Regurgitation

Implications Beyond Dimensions

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Background—Although surgery is indicated in patients with mitral regurgitation (MR) when left ventricular (LV) end-systolic (LVES) dimension is >40 mm, LV ejection fraction may decrease after mitral valve surgery. We hypothesize that significant LV remodeling before surgery is not reflected by standard echocardiographic parameters measured at the base of the heart.

Methods and Results—Ninety-four patients (age, 54±11 years; 38% female) with degenerative isolated MR underwent cine magnetic resonance imaging with tissue tagging and 3-dimensional analysis. In 51 control subjects (age, 44±14 years; 53% female), the relation between LVES volume (LVESV) and LVES dimension was quadratic, whereas in 94 MR patients, this relation was cubic, indicating a greater increase in LVESV per LVES dimension among MR patients. Moreover, magnetic resonance imaging LVESV from summed serial short-axis slices was significantly greater than LVESV assessed with the Bullet formula in MR patients, attributed to a more spherical remodeling distal to the tips of the papillary muscles (P<0.001). Thirty-five patients underwent mitral valve repair per current guideline recommendations. LV ejection fraction decreased from 61±7% to 54±8% (P<0.0001) and maximum shortening decreased significantly below normal at 1 year postoperatively (P<0.0001). Despite normalization of LV stroke volume and LV end-diastolic volume/mass ratio, there was a persistent significant increase in distal LVES 3-dimensional radius/wall thickness ratio and LVESV index after surgery.

Conclusions—Despite apparently preserved LVES dimension, MR patients demonstrate significant spherical mid to apical LVES remodeling that contributes to higher LVESV than predicted by standard geometry-based calculations. Decreased LV strain after surgery suggests that a volumetric analysis of LV remodeling and function may be preferred to evaluate disease progression in isolated MR. (Circulation. 2012;125:2334-2342.)

Key Words: magnetic resonance imaging ■ surgery ■ ventricular dysfunction, left ■ ventricular remodeling

Mitral regurgitation (MR) is a frequent form of valvular disease, representing an important public health burden in the United States. An estimated 2 to 2.5 million people were affected in 2000, a number expected to double by 2030 as a result of population growth and aging.1-3 Isolated MR from myxomatous degeneration of the mitral valve (MV) results in a relatively low-pressure form of volume overload caused by excess volume being ejected through a secondary ejection pathway into the left atrium. Forward cardiac output in MR is preserved by an increase in left ventricular (LV) stroke volume, mediated by augmentation of LV preload (end-diastolic volume), decreased afterload resulting from the relatively low-pressure ejection pathway into the left atrium, and an increase in adrenergic drive. These mechanisms may serve to preserve LV ejection fraction (LVEF), even in the face of increasing LV end-systolic (LVES) dimension (LVESD), volume (LVESV), and LVES wall stress over time. This may explain why, despite adherence to current guideline recommendations,4,5 postoperative LV dysfunction is not uncommon and is associated with increased morbidity and mortality.3,6

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The mechanisms involved in the transition to irreversible cardiomyocyte damage in chronic isolated MR remain elusive. This is compounded by the fact that symptoms of heart failure may be very subtle and LV function and geometry may change significantly in the absence of symptoms. Thus, the success of adherence to echocardiographic guidelines is limited by the
requirement for very close surveillance, which has most likely contributed to the recent reports that patients with isolated MR are not receiving timely surgery, even with advances in surgical repair and minimally invasive surgery.7,8 Studies have reported a decrease in LVEF after MV repair for isolated MR3,9–15 using echocardiography with geometric assumptions based on LV dimensions for LVEF measurements. These findings have resulted in a body of evidence supporting the recommendation for early surgery in the controversy surrounding management of asymptomatic patients with severe MR.9,16–18

It is important to note that echocardiographic follow-up studies in MR have used the standard LVESD measured at the tips of the papillary muscles. We hypothesize that extensive LV apical remodeling in MR hearts, beyond the base and tips of the papillary muscles, contributes to an increasing LVESD that is not appreciated by measuring the LVESD alone. Therefore, in the present investigation, we use cine magnetic resonance imaging (MRI) with tissue tagging and 3-dimensional (3D) data analysis to quantify global and regional LV geometry and function in patients with isolated MR.

Methods

Study Population

Ninety-four patients with moderate to severe MR were recruited from June 2005 to September 2010 at the University of Alabama at Birmingham. All patients referred for surgery had an LVEF >60%, and almost all had an LVESD <40 mm by referral echocardiography studies; the need for surgery was based on conservative clinical judgment of the cardiologist and cardiovascular surgeon at the tertiary referral center. MR severity was documented qualitatively on echocardiography with geometric assumptions based on LV contours at ED and ES were then propagated to the rest of the time frame, and almost all had an LVESD of 30–40 mm. ECG-gated breath-hold MRI was performed on a 1.5-T MRI scanner (Signa, GE Healthcare, Milwaukee, WI) optimized for cardiac imaging. ECG-gated breath-hold steady-state free-precession technique was used to obtain standard (2-, 3-, and 4-chamber long-axis and serial parallel short-axis) views with the following typical parameters: slice thickness of the imaging planes, 8 mm; field of view, 40 cm; scan matrix, 256×128; flip angle, 45°; and repetition/echo times, 3.8/1.6 milliseconds).

MRI Studies

Cine MRI

MRI was performed on a 1.5-T MRI scanner (Signa, GE Healthcare, Milwaukee, WI) optimized for cardiac imaging. ECG-gated breath-hold steady-state free-precession technique was used to obtain standard (2-, 3-, and 4-chamber long-axis and serial parallel short-axis) views with the following typical parameters: slice thickness of the imaging planes, 8 mm; field of view, 40 cm; scan matrix, 256×128; flip angle, 45°; and repetition/echo times, 3.8/1.6 milliseconds).

The 3D LV geometric parameters were measured from endocardial and epicardial contours manually traced on cine magnetic resonance images acquired near end diastole (ED) and end systole (ES). The contours were traced to exclude the papillary muscles. The contours at ED and ES were then propagated to the rest of the time frames with a dual propagation technique.19 LV volumes were computed by summing the volumes defined by the contours in each short-axis slice multiplied by slice thickness. These volumes were referred to as measured volumes in the present study. LV volumetime curve was constructed and differentiated with respect to time to obtain the peak early filling rate.19

The contour data at ED and ES were transformed to a coordinate system aligned along the long axis of the LV and converted to a prolate spheroidal coordinate system as described previously.20 The prolate spheroidal coordinate system has 1 radial coordinate (λ) and 2 angular coordinates (μ, θ). Cubic B-spline surfaces, $\lambda_{\text{endoc}}(\mu, \theta)$ and $\lambda_{\text{epic}}(\mu, \theta)$, were fit to the $\lambda$ coordinates of the endocardial and epicardial contours for each time frame. Each surface used 12 control points in the circumferential direction (θ) and 10 control points in the longitudinal direction (μ). The control points of each surface were computed to minimize the following error function,

$$\epsilon = \sum_{i}[(\lambda(\mu_i, \theta_i) - \lambda_i)^2 + \gamma S(\lambda)]$$

where $\gamma$ is a weight set to 0.1. The first term in the error function is the squared difference between the contour points, $\lambda_i$, and the corresponding surface points, $\lambda(\mu_i, \theta_i)$. The second term is a smoothing function, which penalizes the bending energy of the surface,

$$S(\lambda) = \int_0^\Omega \left( \frac{\partial^2 \lambda}{\partial \mu^2} \right)^2 + 2 \left( \frac{\partial^2 \lambda}{\partial \mu \partial \theta} \right)^2 + \left( \frac{\partial^2 \lambda}{\partial \theta^2} \right)^2 \, d\Omega$$

where $\Omega$ is the domain of the surface. The 3D endocardial circumferential curvatures were then computed from standard formulas21 at the wall segments as previously defined (excluding the apex). Two-dimensional apex curvatures were computed as the average of apex curvatures calculated from endocardial contours drawn on the 4- and 2-chamber view images with the standard formula.21 Sphericity index was defined as the ratio of LV long-axis length to LV inner diameter.23 A smaller sphericity index indicates greater sphericity. The 3D wall thickness was computed at all wall segments (excluding the apex) by measuring the 3D distance from a point on the epicardial surface to the closest point on the endocardial surface along a line perpendicular to the epicardial surface. Radius of curvature to wall thickness ratio (R/T) was computed by the reciprocal of the product of the endocardial circumferential curvature and 3D wall thickness.

Tagged MRI

Tagged MRI was acquired on the same scanner using the same slice prescription as cine MRI with the following typical parameters: repetition/echo times, 8/4.2 milliseconds; tag spacing, 7 mm; trigger time, 10 milliseconds from the R wave; and flip angle, 10°. Tag lines were tracked and edited if necessary by experts. LVESV maximum shortening strain was computed at all wall segments (excluding the apex) by fitting a B-spline deformation model in prolate spheroidal coordinates to the tag line data.23

Bullet Formula

LVESV (in milliliters) was also calculated from LVESD (millimeters) and LVES length (centimeters) with the Bullet formula24,27 as follows:

$$\text{LVESV} = 0.83 \times \pi \times \left( \frac{\text{LVESD}^2}{20} \right) \times L$$

where L is the length of LV measured from apex to the tip of the papillary muscle. This volume was referred to as calculated volume in the present study.
Statistical Analysis
The Student 2-sample t test (for continuous variables) and Fisher exact test (for categorical variables) were conducted to compare the control group (n=51) and the MR group (n=94) in terms of demographic, geometric, and functional variables.

Regression analyses between LVESV and LVESD were performed in control subjects and MR patients. Model adequacy checking showed that the model was not linear for both groups. Therefore, square root transformation was performed to the control group, which eliminated the nonlinearity problem. For the MR group, square root transformation did not resolve the nonlinearity problem. Thus, cubic root transformation was performed with which the test showed proof of linearity of the model. The Student paired t test was performed to compare the measured LVESV by summing the volumes defined by contours multiplied by slice thickness versus LVESV calculated by the Bullet formula. Regression analysis was also performed to test the association between the difference of measured and calculated LVESV and 3D distal LV circumferential curvature. Model adequacy checking showed that the model was not linear. Thus, square root transformation was performed, which eliminated the nonlinearity problem.

One-way ANOVA was used to perform group-wise comparisons among control subjects and MR patients with LVESD <37 and ≥37 mm (corresponding to more than the mean±1 SD of the LVESD of the control group; moreover, the mean LVESD in the MR group was 37 mm). The P values of all pair-wise differences were adjusted with the Tukey-Kramer procedure.

Comparisons of the MRI variables among control subjects and MR patients before and 12 months after surgery were performed with a mixed model via PROC MIXED. The repeated measures of the MR patients before and after surgery were accounted for by an assumed compound symmetry correlation structure. To avoid inflating the probability of a type I error, the Bonferroni-Holm step-down test procedure was used to adjust the significance level accordingly.

Model adequacy checking was performed for all models. Linearity was checked by plotting the model residuals versus the dependent variable to look for any curve band or nonlinear pattern. The Shapiro-Wilk test was performed for normality test. Log transformation, square root transformation, or cubic root transformation was performed if there were outliers, if the normality assumption was not valid, or if the homogeneity assumption was violated as appropriate.

A value of P<0.05 was considered statistically significant. We also conducted a general linear model for LV functional parameters to adjust for age and stroke volume indexes (volumes normalized to body surface area), as well as higher LVEDD and LVESD, compared with control subjects. However, there were no differences in LV lengths at both ED and ES in MR patients compared with control subjects. MRI-derived LVEF was significantly different between the 2 groups. LV mass index and LVEDV/mass ratio were significantly increased in MR patients compared with control subjects. Peak early filling rate was significantly higher in the MR group than in control subjects (P<0.0001).

Figure 1A shows 2 representative examples from a control subject and an MR patient. Both hearts had the same LVEDS (37 mm) and similar LVES length; however, the MR LV had marked spherical remodeling demonstrated by the color-coded circumferential curvature grid from base to distal LV depicted by lesser circumferential curvature (red) in the MR and greater circumferential curvature in the control (yellow). The LVEF of the MR heart was 85 mL and that of the normal heart was 49 mL. Figure 1B demonstrates LV remodeling in an MR compared with a control heart.

Figure 2 demonstrates the relation between LVESV and LVEDV in the MR (Figure 2A) and control (Figure 2B) groups. In the MR group, this relation was cubic [LVESV=(2.68+0.12×LVEDV)2; P<0.0001], whereas this relation was quadratic in control subjects [LVESV=(2.68+0.12×LVEDV)2; P<0.0001]. Of particular interest, LVESV calculated from LVEDV with the Bullet formula demonstrated no significant difference from the measured LVESV by summation of the serial short-axis images in control subjects. However, the Bullet

Results
Clinical Characteristics
Clinical and MRI characteristics of the control subjects and 94 MR patients are outlined in Table 1. The 2 groups had a similar age range (20–70 and 25–76 years, respectively). However, the MR group was significantly older than the control group. There were no significant differences in body surface area and sex between the 2 groups. Heart rate and systolic and diastolic blood pressures were also similar in the 2 groups.

MRI-Derived Variables in Control Subjects and MR Patients
As expected, MR patients had significant increases in LV end-diastolic (LVED) volume (LVEDV), LVESV, and LV stroke volume indexes (volumes normalized to body surface area), as well as higher LVEDD and LVESD, compared with control subjects. However, there were no differences in LV lengths at both ED and ES in MR patients compared with control subjects. MRI-derived LVEF was significantly different between the 2 groups. LV mass index and LVEDV/mass ratio were significantly increased in MR patients compared with control subjects. Peak early filling rate was significantly higher in the MR group than in control subjects (P<0.0001).

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formula significantly underestimated LVESV in the MR group. This difference between the measured and calculated LVESVs in MR was significantly negatively correlated with the 3D circumferential curvature at the distal LV ($P<0.0001$), as shown in Figure 2C.

**Effect of LVESD on Baseline LV Geometry and Function**

All 94 MR patients were divided into 2 groups: LVESD <37 mm (n=48) and LVESD ≥37 mm (n=46). The cutoff LVESD of 37 mm was selected corresponding to more than the mean+1 SD of the LVESD of the control group; Moreover, the mean LVESD of MR was 37 mm. Table 2 shows the comparisons between control subjects and the 2 MR groups in LVES length, volume index, and global and 2-dimensional apical sphericity. With LVESD <37 mm, there was no increase in length; however, LVESV, LV global, and 2-dimensional apical sphericity were significantly higher than in control subjects. With LVESD ≥37 mm, LVESV was further increased and the apex curvature remained similarly lower than in control subjects; with no commensurate increase in LV length, LV global sphericity was further increased.

Figure 3 demonstrates the differences in 3D LV geometry and maximum shortening from the base, mid, and distal LV at ED and ES among control subjects, MR patients with LVESD <37 mm, and MR patients with LVESD ≥37 mm. In the MR patients, LVED circumferential curvature decreased and R/T ratio increased from the base to distal LV compared with control subjects. These changes were more significant in MR patients with LVESD ≥37 mm than in MR patients. The difference between the measured LVESV and LVESV calculated from the Bullet formula in MR are plotted vs LVES circumferential curvature at the distal LV. The solid back line represents the fitted model.
patients with LVESD <37 mm. In MR patients with LVESD ≥37 mm, LVES circumferential curvature was significantly lower at the LV base (0.44 ± 0.04), mid (0.47 ± 0.05), and distal LV (0.59 ± 0.08) compared with MR patients with LVESD <37 mm and control subjects (P < 0.0001 for base, mid, and distal LV). LVES R/T ratio was significantly increased in MR patients with LVESD ≥37 mm (1.86 ± 0.4 at base, 2.03 ± 0.4 at mid, and 2.01 ± 0.5 at distal LV) compared with both MR patients with LVESD <37 mm (1.48 ± 0.3 at base, 1.67 ± 0.4 at mid, and 1.69 ± 0.4 at distal LV; P < 0.0001) and control subjects (1.64 ± 0.4 at base, 1.61 ± 0.4 at mid, 1.48 ± 0.4 at distal LV; P < 0.0001). However, in MR patients with LVESD <37 mm, LVES R/T ratio did not differ from control at all segments. There were no significant differences among all 3 groups in LV maximum shortening strain after adjustment for age and systolic blood pressure.

LV Geometry and Function After MV Repair

Table 3 shows the clinical characteristics of control subjects, preoperative MR patients, and 12-month postoperative MR patients. The mean age of the surgical MR group was significantly higher and the percentage of female patients was significantly smaller in the MR group compared with control subjects. Therefore, comparisons of LV functional parameters among the groups were adjusted for an age effect. Control subjects and surgical MR patients before and after surgery had matched body surface area, heart rate, and systolic and diastolic blood pressures. Before surgery, 20 patients were in New York Heart Association functional class I (57%), 14 patients were in New York Heart Association class II (40%), and 1 patient was in New York Heart Association class III (3%).

One year after the surgery, nearly all patients were classified as New York Heart Association class I, whereas 1 patient was classified as New York Heart Association class II.

Table 2. Left Ventricular Geometry in Mitral Regurgitation Patients With Left Ventricular End-Systolic Dimension <37 and ≥37 mm

<table>
<thead>
<tr>
<th></th>
<th>Control (n=51)</th>
<th>LVES Dimension &lt;37 mm (n=48)</th>
<th>LVES Dimension ≥37 mm (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVES length, cm</td>
<td>6.81 ± 0.66</td>
<td>6.73 ± 0.87</td>
<td>7.14 ± 0.69†</td>
</tr>
<tr>
<td>LVES sphericity index</td>
<td>1.95 ± 0.26</td>
<td>1.82 ± 0.23*</td>
<td>1.64 ± 0.21†</td>
</tr>
<tr>
<td>LVES volume index, mL/m²</td>
<td>25 ± 6</td>
<td>34 ± 9*</td>
<td>48 ± 13†</td>
</tr>
<tr>
<td>2D LV apex curvature, 1/cm‡</td>
<td>2.93 ± 1.13</td>
<td>1.89 ± 0.48*</td>
<td>1.84 ± 1.54*</td>
</tr>
</tbody>
</table>

MR indicates mitral regurgitation; LVES, left ventricular end-systolic dimension; and 2D, 2-dimensional. Values are mean ± SD.

*P < 0.05 vs control subjects.
†P < 0.05 vs MR patients with LVESD <37 mm.
‡Log transformation was performed.

Figure 3. Three-dimensional left ventricular (LV) end-diastolic (LVED; left column) and LV end-systolic (LVES; right column) geometry with maximum shortening in the control subjects (n=51) and mitral regurgitation (MR) patients (n=94) divided into those with LVES dimension (LVESD) <37 and ≥37 mm. These data demonstrate progressive global LVED and LVES remodeling in both groups of MR patients compared with control subjects. However, LV maximum shortening remains normal or even supranormal in both MR groups. R/T indicates radius of curvature to wall thickness ratio.

*P < 0.05 vs control subjects; †P < 0.05 vs MR patients with preoperative LVESD <37 mm.
LVESD, LVEDV index, LV mass index were significantly decreased at all levels after surgery. In MR patients with LVESD \( \geq 37 \text{ mm} \), LVED and LVES circumferential curvatures were decreased before and improved after surgery but remained below normal at ES. In contrast, the LVED R/T ratio returned to normal whereas LVES R/T ratio remained above that of control subjects after surgery.

Figure 6 shows the change in maximum shortening after surgery in the MR patients with LVEDV <37 and \( \geq 37 \text{ mm} \). Although the LVES R/T ratio in MR patients with LVEDV <37 mm did not differ from that in control subjects before and after surgery, maximum shortening was significantly decreased from mid to distal LV after surgery. In MR patients with LVEDV \( \geq 37 \text{ mm} \), LVES maximum shortening was decreased at all levels after surgery.

Incidence of Postoperative LV Dysfunction
Table 4 shows that among the 35 surgical MR patients, 11 patients (31%) had postoperative LV dysfunction (defined as LVEF \(<50\%\)). Two of them had preoperative LVESD \(<37 \text{ mm} \), whereas 9 of them had preoperative LVESD \( \geq 37 \text{ mm} \). The incidence of postoperative LV dysfunction in MR patients with LVEDV <37 mm (14\%) was lower than that in MR patients with LVEDV \( \geq 37 \text{ mm} \) (43\%; \( P=0.0616 \)). There was no significant difference between the two groups.
were 10 surgical MR patients in LVESD range of 37 to 40 mm, and 2 of them (20%) had postoperative LV dysfunction.

**Discussion**

A major finding of the present investigation is that LVESD, although commonly used to assess the extent of LV remodeling in patients with isolated MR, does not accurately reflect the extent of LV remodeling, largely because of spherical LV remodeling from the mid to apical LV. Furthermore, conservative management of patients with isolated MR based on standard dimensions was associated with a significant decrease in LVEF and maximum strain after MV repair. Compared with a group of control subjects with a similar age range, the relation of LVESD to LVESV is cubic in MR patients in contrast to a quadratic relation in control subjects, indicating a greater increase in LVESV per unit of LVESD in MR patients compared with control subjects. The Bullet formula, which is commonly used to calculate LV volumes, significantly underestimates MR LVESV based on the LVESD measured at the tips of the papillary muscles. The extra volume can be attributed to the extensive LV mid to distal spherical remodeling, which is not accounted for in the Bullet formula. The importance of this finding is that although LVESD remains below the accepted target of 40 mm for surgical intervention of isolated MR, its associated LVESV can range as high as twice that of the normal control subjects. This finding therefore identifies a volumetric parameter (LVESV) that more suitably characterizes overall LV remodeling in isolated MR.

The variance in LVESV in MR is attributed to LV mid to apical spherical remodeling that is evident even in the patients with LVESD <37 mm; however, the LVES R/T ratio remains normal, suggesting a more compensated hypertrophy in this group. It is of interest that even with an increase in LVESV in the MR patients with LVESD ≥37 mm group, there is not a commensurate LV elongation, which is consistent with a more global spherical LV remodeling. This is also associated with an increase in the LVES R/T ratio at all LV segments from base to distal LV, a marker of increased wall stress. Despite this progression of adverse LV remodeling, maximum shortening from the base to distal LV remains normal in both groups. This finding is in agreement with the known favorable loading conditions of an increase in LV preload and excessive adrenergic drive, combined with a facilitation of ejection through a secondary ejection pathway into left atrium in isolated MR.

In an attempt to determine the functional importance of these geometric changes in isolated chronic MR, we evaluated LV geometry and function in 35 patients from this cohort before and after surgery. These data demonstrate progressive LV remodeling at end systole that is not normalized after surgery in the MR patients with preoperative LVESD ≥37 mm, whereas it is normalized after surgery in MR patients with preoperative LVESD <37 mm. R/T indicates radius of curvature to wall thickness ratio. *P<0.05 vs control subjects; †P<0.05 vs preoperative MR.

**Figure 5.** Comparison of left ventricular (LV) end-systolic (LVES) geometric remodeling in control subjects and in surgical mitral regurgitation (MR) patients with preoperative LVES dimension (LVESD) <37 and ≥37 mm before and after surgery. These data demonstrate progressive LV remodeling at end systole that is not normalized after surgery in the MR patients with preoperative LVESD ≥37 mm, whereas it is normalized after surgery in MR patients with preoperative LVESD <37 mm. R/T indicates radius of curvature to wall thickness ratio. *P<0.05 vs control subjects; †P<0.05 vs preoperative MR.

**Figure 6.** Comparison of left ventricular end-systolic (LVES) maximum shortening in control subjects and in surgical mitral regurgitation (MR) patients with preoperative LVES dimension (LVESD) <37 and ≥37 mm before and after surgery. These data demonstrate maximum shortening is decreased below normal in both groups of MR patients except that LVES maximum shortening is preserved at the base in patients with preoperative LVESD <37 mm. *P<0.05 vs control subjects; †P<0.05 vs preoperative MR.
interest in isolated MR, Ozdogan et al.33 and Cawley and LVES dimension reaches 40 mm. In support of a volumetric analysis in isolated MR, Ozdogan et al. and Cawley and LVESD indicates left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction. *P = 0.0616 vs mitral regurgitation patients with preoperative LVESD <37 mm.

LV remodeling before surgery was associated with a significant decrease in LV maximum shortening after surgery. It is important to note that even in patients with MRI-derived LVEF >60% before MV repair, directional changes after surgery remained the same (Table I and Figures I–III in the online-only Data Supplement). The decrease in LVEF and LV maximum strain from preoperative to postoperative values persisted in patients with MRI-derived LVEF >60% before MV repair (Table I and Figure III in the online-only Data Supplement). We have recently reported the finding of excessive cardiomyocyte oxidative stress, myofibrillar degeneration, and lipofuscin accumulation, which collectively may result in irreversible cardiomyocyte dysfunction in patients with preoperative LVEF >60%.6 Taken together, the presence of adverse LV remodeling before surgery is associated with decreased maximal shortening 1 year after surgery.

Dujardin et al.12 have demonstrated an exponential correlation between LVESD and LVESV using echocardiography, especially for enlarged ventricles. The present study used MRI with 3D analysis and determined that the relation between LVESV and LVESD is cubic in MR and quadratic in control subjects. Apical spherical remodeling appears to occur before a significant change being detected at the base. Thus, severely elevated LVES volume can occur before LVES dimension reaches 40 mm. In support of a volumetric analysis in isolated MR, Ozdogan et al.33 and Cawley and Otto44 have also suggested that the use of a geometry-independent volume assessment with MRI is preferred for LVEF measurement in timing of surgery.

The present study is limited in that the follow-up is only 1 year in a small number of patients. Previous reports in patients with aortic regurgitation and aortic stenosis demonstrate that there is continued improvement for years after surgery.35,36 Despite a small sample size, this represents a homogeneous population that does not have evidence of coronary artery disease by coronary angiography. All patients being referred for surgery had LVEF >60%, and almost all had LVESD <40 mm by referral echocardiography studies; the need for surgery was based on conservative clinical judgment. Subsequent MRI and 3D analysis uncovered some patients with LVEF <60%, highlighting the need for a more comprehensive volumetric analysis of LV remodeling. Finally, although we are convinced that the surrogate outcome of LVES volume will be strongly related to the important clinical outcomes, it is clear that this question can be addressed only in a clinical trial testing the comparative effectiveness of LV dimensions versus MRI- or 3D echocardiography–derived LV volume on clinical outcomes.

The results of the present study uncover greater LV remodeling that contributes to higher LVES volume and corresponds to decreased LV shortening strain after surgery, suggesting that simple geometry-based assessments of volume may underestimate LV dysfunction in isolated MR. The present investigation demonstrates the potential for high variability of spherical remodeling from the LV mid to apex, beyond the conventional point of LVESD measurement, that contributes to the increase of LVES volume. Importantly, this adverse LV remodeling before surgery is associated with a reduction in maximum shortening. These results suggest that a more detailed geometric LV analysis and volume-based assessment at ES provide a superior evaluation of extent of LV remodeling and may serve as better markers for optimal timing of surgery in the patient with isolated MR to maximally preserve postoperative LV function.

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Disclosures

None.

References

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**CLINICAL PERSPECTIVE**

Although surgery is indicated in patients with mitral regurgitation when left ventricular (LV) end-systolic dimension is >40 mm, LV ejection fraction may decrease after mitral valve surgery. A major finding of the present investigation is that LV end-systolic dimension does not accurately reflect the extent of LV remodeling, largely because of spherical LV remodeling from the mid to apical LV by magnetic resonance imaging with 3-dimensional analysis. This study demonstrates that even when LV end-systolic dimension remains below the accepted target of 40 mm for surgical intervention of isolated mitral regurgitation, its associated LV end-systolic volume can range as high as twice that of normal control subjects. Magnetic resonance imaging with 3-dimensional analysis– or 3-dimensional echocardiography–derived LV volumes may be preferred to evaluate disease progression in isolated mitral regurgitation.
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Supplemental Table 1. Clinical characteristics of surgical patients with mitral valve repair and MRI-derived LVEF > 60% prior to surgery

<table>
<thead>
<tr>
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<th>Control (n=51)</th>
<th>Pre-operative (n=20)</th>
<th>Post-operative (n=20)</th>
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<tbody>
<tr>
<td>Age, year</td>
<td>44±14</td>
<td>54±8*</td>
<td>55±8*</td>
</tr>
<tr>
<td>% Female</td>
<td>53</td>
<td>15*</td>
<td>15*</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.9±0.24</td>
<td>2.01±0.23</td>
<td>2.01±0.21</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>67±12</td>
<td>68±10</td>
<td>70±11</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>118±13</td>
<td>125±13</td>
<td>124±12</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg‡</td>
<td>75±10</td>
<td>77±9</td>
<td>79±9</td>
</tr>
<tr>
<td>LV ED volume index, ml/m²‡</td>
<td>69±10</td>
<td>112±24*</td>
<td>76±14†</td>
</tr>
<tr>
<td>LV ES volume index, ml/m²‡</td>
<td>25±7</td>
<td>39±10*</td>
<td>33±9*†</td>
</tr>
<tr>
<td>LV SV volume index, ml/m²‡</td>
<td>44±7</td>
<td>73±16*</td>
<td>44±8†</td>
</tr>
<tr>
<td>LV EF, %‡</td>
<td>64±7</td>
<td>65±4</td>
<td>57±7*†</td>
</tr>
<tr>
<td>LV ED dimension, mm‡</td>
<td>49±4</td>
<td>59±7*</td>
<td>49±5†</td>
</tr>
<tr>
<td>LV ES dimension, mm‡</td>
<td>32±4</td>
<td>37±5*</td>
<td>34±7*†</td>
</tr>
<tr>
<td>LV ED mass index, g/m²</td>
<td>50±10</td>
<td>70±13*</td>
<td>56±11†</td>
</tr>
<tr>
<td>LV ED volume/mass, ml/g</td>
<td>1.45±0.38</td>
<td>1.62±0.26</td>
<td>1.41±0.35†</td>
</tr>
<tr>
<td>LV ES R/T ratio‡</td>
<td>1.48±0.40</td>
<td>1.65±0.54</td>
<td>1.71±0.65</td>
</tr>
<tr>
<td>Peak early filling rate, ml/sec‡</td>
<td>378±110</td>
<td>686±273*</td>
<td>288±91†</td>
</tr>
</tbody>
</table>

Values are n or mean±SD. BP: blood pressure; R/T ratio: radius /wall thickness measured at distal LV; *: P<0.05 vs. control; †: P<0.05 vs. pre-operative MR; ‡: log transformation was performed. Comparison results were adjusted for age.
Supplemental Figure 1. Comparison of LV end-diastolic (ED) geometric remodeling in controls and in surgical MR patients (patients with MRI-derived LVEF<60% prior to surgery are excluded) with pre-operative LVESD < and ≥ 37mm before and after surgery. These data demonstrate progressive LV remodeling at ED in the two MR groups and their recovery after surgery. LVED R/T ratio is normalized after surgery in both MR groups. Circumferential curvatures in MR LVESD<37mm are normalized after surgery while in MR LVESD≥37mm, circumferential curvatures are increased yet not normalized. *: P<0.05 vs. controls; †: P<0.05 vs. pre-operative MR.
Supplemental Figure 2. Comparison of LV end-systolic (ES) geometric remodeling in controls and in surgical MR patients (patients with MRI-derived LVEF<60% prior to surgery are excluded) with pre-operative LVESD < and ≥ 37mm before and after surgery.

These data demonstrate progressive LV remodeling at ES that is not normalized after surgery in the MR patients with pre-operative LVESD ≥ 37mm, while it is normalized after surgery in MR patients with pre-operative LVESD<37mm. *: P<0.05 vs. controls; †: P<0.05 vs. pre-operative MR.
Supplemental Figure 3. Comparison of LV end-systolic (ES) maximum shortening in controls and in surgical MR patients (patients with MRI-derived LVEF<60% prior to surgery are excluded) with pre-operative LVESD < and ≥ 37mm before and after surgery. These data demonstrate that maximum shortening is decreased below normal in both groups of MR patients. Moreover, LVES maximum shortening in patients with pre-operative LVESD ≥37 mm is significantly decreased post-operatively vs. pre-operatively. *: P<0.05 vs. controls; †: P<0.05 vs. pre-operative MR.