Mechanism of Recurrent Ischemic Mitral Regurgitation After Annuloplasty
Continued LV Remodeling as a Moving Target
Judy Hung, MD; Lampros Papakostas, MD; Stephen A. Tahta, MD; Bruce G. Hardy, MD; Bruce A. Bollen, MD; Carlos M. Duran, MD, PhD; Robert A. Levine, MD

Background—Patients who undergo ring annuloplasty for ischemic mitral regurgitation (MR) often have persistent or recurrent MR. This may relate to persistent leaflet tethering from left ventricle (LV) dilatation that is not relieved by ring annuloplasty. Therefore, the purpose of this study was to test the hypothesis that recurrent MR in patients after ring annuloplasty relates to continued LV remodeling.

Methods and Results—Serial echocardiograms were reviewed in 30 patients (aged 72±11 years) who showed recurrent MR late (47±27 months) versus early (3.8±5.8 months) after ring annuloplasty for ischemic MR during coronary artery bypass grafting without interval infarction. Patients with intrinsic mitral valve disease were excluded. Echocardiographic measures of MR (vena contracta and jet area/left atrial area) and LV remodeling (LV dimensions, volumes, and sphericity) were assessed at each stage. The degree of MR increased from mild to moderate, on average, from early to late postoperative stages, without significant change in LV ejection fraction. Changes in MR paralleled increases in LV volumes and sphericity index at end-systole and end-diastole. The only independent predictor of late postoperative MR was LV sphericity index at end-systole.

Conclusions—Recurrent MR late after ring annuloplasty is associated with continued LV remodeling, emphasizing its dynamic relation to the LV.

Key Words: mitral regurgitation □ ring annuloplasty □ left ventricle remodeling

Ischemic mitral regurgitation (MR) results from remodeling of the ischemic left ventricle (LV), leading to displacement of the papillary muscles, annular dilatation, and therefore tethering of the mitral leaflets. This restricts mitral leaflet closure, preventing proper coaptation at the annulus.1–13 A standard therapeutic approach to relieve ischemic MR is a ring annuloplasty,14–19 which reduces mitral annular area by bringing the dilated posterior annulus anteriorly to reduce the anterior–posterior dimension and bring the leaflets into apposition. However, the long-term efficacy of ring annuloplasty is unclear. Recent studies in several centers have demonstrated that MR can persist or recur after ring annuloplasty, consistent with clinical observations.20–24 Given the fundamental mechanism of mitral leaflet tethering, ring annuloplasty addresses only the annular end and does not directly address tethering by the remodeled ventricle. Remodeling is progressive,25–30 so that initial annular compensation for ventricular dilatation may not be durable. Therefore, the purpose of our study was to test the hypothesis that recurrent MR after ring annuloplasty relates to continued LV remodeling.

Methods
To explore the mechanism underlying persistent or recurrent MR after ring annuloplasty, we specifically targeted patients with persistent or recurrent MR after ring annuloplasty and CABG. The study population consisted of patients undergoing coronary artery bypass and mitral ring annuloplasty for moderate to severe MR at 2 institutions, International Heart Institute of Montana, University of Montana, Missoula, and Massachusetts General Hospital, Boston, for a 2-year period from 1996 to 1998. Rigorous criteria were applied to exclude patients with intrinsic mitral valve disease to select for a relatively homogeneous patient population with ischemic MR. Patients with mitral valve thickening, prolapse, annular calcification, vegetation, fenestration, and rheumatic mitral valve changes were excluded. Patients with echocardiograms inadequate for quantitative analysis were also excluded.

Echocardiographic Analysis
Echocardiograms were analyzed offline on a Philips 7500 SONOS machine (Philips Medical Systems). Quantitation of MR was performed at the preoperative, intra-operative, early postoperative, and late postoperative stages. Analysis of LV remodeling changes was performed at preoperative, early postoperative, and late postoperative stages.
spherical the LV becomes, the greater the degree of papillary muscle tethering because the more atrial of area ratio. The width of the vena contracta or the narrowest jet origin was measured in a long-axis view perpendicular to the coaptation line, typically the parasternal or apical long-axis views. The maximal jet area-to-left atrial area ratio was measured in the parasternal and apical view. An average was taken of 3 cardiac cycles for each MR measurement.

LV Volumes
LV volumes were calculated using the biplane Simpson method from the apical 4- and 2-chamber views. The sphericity index was a surrogate measure of the degree of leaflet tethering because the more spherical the LV becomes, the greater the degree of papillary muscle displacement that exerts tethering on the leaflets. Papillary Muscle Displacement Distance Outside the Annular Ring
Papillary muscles normally exert forces perpendicular to the leaflet surfaces to oppose left ventricular forces. However, if the papillary muscles are displaced in a posterior and/or lateral direction, they will apply distracting forces that prevent normal leaflet coaptation. The projected papillary muscle displacement (PM-Dis) outside of the annular ring is a measure of the degree of displacement that can generate distraction forces by the papillary muscles. To measure this projected papillary displacement, a perpendicular line is drawn from the tip of the papillary muscle to the mitral annular line in a long-axis view. The distance from this projection to the mitral ring itself is the PM-Dis (Figure 1).

Statistical Analysis
Repeated measures ANOVA was performed to determine differences among stages (preoperative, early postoperative, and late postoperative), with significance at $P<0.05$. To study the progression of MR in different patients, quantitative measures of MR were normalized for the preoperative degree of MR at baseline for the multiple linear regression analysis. The determinants of MR at the late postoperative stage were explored by multiple linear regression in a step-wise manner, entering LV end-diastolic and end-systolic volumes, LV ejection fraction, sphericity index at end-diastole and end-systole, ring type, ring size, and early postoperative MR. Differences in late postoperative MR, normalized to initial MR (both maximal jet area-to-left atrial area ratio and vena contracta) were compared among ring types (complete semi-rigid, complete flexible, and incomplete flexible) by ANOVA. All statistical analysis was performed on SAS 6.12.

Results
Patient Characteristics
The study population consisted of 30 patients (18 males and 12 females) with a mean age of 72 ± 11 years. All underwent coronary artery bypass and mitral ring annuloplasty for moderate or severe MR. All patients had complete revascularization. Preoperative echocardiograms were performed at an average of 0.7 ± 1 month, early postoperative echocardiograms were performed at an average of 3.8 ± 5.8 months, and the later postoperative echocardiograms were performed at an average of 47 ± 27 months. After bypass surgery and ring annuloplasty, no patient had a subsequent myocardial infarction or required additional revascularization.

Patients were managed medically after bypass surgery with standard heart failure medications including beta-blockers, angiotensin-converting enzyme inhibitors, and diuretics. The average ring size was 30 ± 2 mm (range 26 to 34 mm). Forty percent were Carpentier-Edwards Physio rings, 33% were Duran-Medtronic Flexible rings, 14% Cosgrove rings, and 13% were St. Jude Medical Seguin rings.

Change in MR
At the preoperative stage, the average vena contracta width was 0.72 ± 0.30 cm, corresponding to moderate to severe MR. At the intra-operative stage, immediately after bypass and ring annuloplasty, the average MR degree decreased to mild (vena contracta 0.24 ± 0.24 cm). Frequently at the end of the operation, the MR was undetectable. At the early postoperative stage, the VC had increased to 0.35 ± 0.31 cm,
and at the time of the late postoperative stage, the average VC had increased to 0.50±0.37 cm (Figure 2). At the early postoperative stage, the majority of patients had only mild MR (70%), with only 30% having moderate or severe MR. However, at the time of the late postoperative stage, these proportions were reversed, with only 28% having mild MR and 72% have moderate or severe MR (Table 1). A similar pattern was found with MR quantification by jet area/left atrial area ratio (Figure 2).

Changes in LV Volumes and Sphericity
The changes in MR were paralleled by changes in LV volumes (Figure 3) without concomitant change in LVEF (Figure 4). There was initial reduction in LV volumes at the early postoperative stage, followed by a significant increase at the late postoperative stage (Figure 3). Changes in sphericity index mirrored those of MR and LV volumes. There was an initial reduction in sphericity index both at end-diastole and end-systole in the early postoperative stage with a late increase, exceeding the preoperative value, consistent with further remodeling after ring annuloplasty (Figure 5). Table 2 summarizes the MR, LV volume, and LV sphericity changes. Figure 6 shows an example of the changes in LV volume and shape that occurred in a patient. At the early postoperative stage, the LV, although dilated with a left ventricular dimension of 58 mm, retains its bullet shape. At this early stage, the patient has little leaflet tethering and only mild MR (Figure 6A and 6B). However, at the late postoperative stage, the LV has further dilated (left ventricular dimension=73 mm) and become more spherical, resulting in increased tethering of the mitral leaflets. The posterior leaflet has become restricted and tethered toward the posterior papillary muscle region as the wall underlying that papillary muscle bulges further posteriorly and outward (Figure 6C). This increased tethering has resulted in moderate MR (Figure 6D).

The increases in sphericity index at the late postoperative stage reflected increased tethering on the mitral valve and greater displacement of the papillary muscles. Ring annuloplasty can potentially exacerbate papillary muscle displacement by increasing the distance from the papillary muscle to the mitral annulus (Figure 1). This projected PM-Dis increased from the early to the late postoperative stage, consistent with increased displacement of the papillary muscle outside the mitral annulus (Figure 1A).

Stepwise multiple linear regression analysis demonstrated that late postoperative end-systolic sphericity index was the only predictor of late postoperative MR ($P=0.004$, $R^2=0.41$ for vena contracta and $P=0.002$, $R^2=0.43$ for jet area/left atrial area ratio). Ring size and type of ring were not predictors of late postoperative MR in this model. ANOVA showed no significant difference in late postoperative MR among ring types (complete semi-rigid, complete, or incomplete flexible rings; $P=0.11$ for maximal jet area/left atrial

<table>
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<th>TABLE 1. MR Degree by Stage</th>
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<tr>
<td>Degree of MR</td>
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<tr>
<td>Mild or less</td>
</tr>
<tr>
<td>Moderate</td>
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<td>Severe</td>
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MR indicates mitral regurgitation.

Figure 2. This shows the changes in MR as measured by vena contracta (VC) (A) or jet area/left atrial area ratio (B) at preoperative, intra-operative, early postoperative, and late postoperative stages. Reported as mean±SEM.

Figure 3. This shows the changes in LV end-diastolic (EDV) (A) and end-systolic (ESV) (B) at preoperative, early postoperative, and late postoperative stages. Reported as mean±SEM.
area ratio, \( P = 0.15 \) for vena contracta), although there are limited numbers within each subgroup.

**Discussion**

This study shows that recurrence of MR after ring annuloplasty is associated with continued LV remodeling, as demonstrated by increases in LV volumes and sphericity, which parallel the increases in MR after ring annuloplasty. Multiple linear regression analysis demonstrated that end-systolic sphericity index, which reflects global LV shape and volume, predicted late postoperative MR. Of note is that MR progression occurred from an early postoperative study acquired several months, on average, after the surgery, and therefore is not subject to the altered loading conditions widely recognized as reducing apparent MR severity intraoperatively.38

**Mechanistic Insights**

These results highlight the limitations of ring annuloplasty as sole therapy, because it reduces tethering only at the annular and not at the ventricular end. Progressive ventricular remodeling in ischemic heart disease can therefore increase tethering and worsen MR despite initial reduction. The ability of ring annuloplasty to compensate for ventricular tethering can then be overwhelmed by further ventricular remodeling.

This limitation is reflected by the increases in the projected papillary muscle displacement outside the annular ring (PM-Dis) from early to late postoperative stages. This displacement outside the annular ring has the potential to produce forces that distract the leaflets from effective coaptation.10,37 The papillary muscles are normally aligned directly over the mitral annular area to exert a perpendicular force on the mitral leaflets, producing normal coaptation.37 With ischemic LV distortion and lateral and/or posterior papillary muscle displacement, the papillary muscles now exert forces in an oblique direction, resulting in increased tethering and ineffective coaptation. Whether the papillary muscle is “in or out” of the mitral ring plane as assessed in standard 2-dimensional echocardiographic views may provide a rapid visual estimation of the degree of tethering.

**Clinical Implications**

Although successful acutely, ring annuloplasty did not prevent the recurrence of MR in these patients, especially when there was further ventricular remodeling. In fact, the majority of patients had mild MR at the time of the early postoperative study. Mild MR therefore may not be benign in this patient population if it contributes to continued remodeling, resulting in a vicious cycle in which MR begets more MR. There was no correlation between ring size or type and development of MR at the late postoperative stage in this study. However, in this study, markedly undersized rings were not placed, and the usefulness of restrictive or undersized ring annuloplasty warrants further investigation.39–41

One point of caution with annular ring reduction is demonstrated in Figure 1. Reducing annular size can potentially shift the posterior annulus farther anteriorly, increasing its displacement relative to the papillary muscles, which may actually, in principle, exacerbate tethering. This concern is highlighted by the common observation in patients with annular ring reduction that the posterior leaflet, under increased tethering, becomes nearly rigid, converting the valve effectively into a unicuspid valve with a restricted anterior leaflet as well.42

In addition to the use of rings, which may be undersized to compensate for persistent tethering, methods that reinforce
the mitral annulus in the septal–lateral (anterior–posterior) dimensions also merit further exploration. The development and evaluation of therapies that directly address tethering may provide a more efficacious treatment for ischemic MR, either independently or more comprehensively in conjunction with ring annuloplasty.

Limitations
This is a mechanistic study designed specifically to examine the mechanism underlying recurrent MR after ring annuloplasty and was not designed to address the overall frequency of recurrent MR. Tahta et al24 in a large single-center surgical series have reported an incidence of ≈30% of recurrent moderate or greater MR over a 3-year follow-up period, with other smaller studies reporting higher frequencies of recurrent MR (moderate or greater) after ring annuloplasty. Future work is indicated to determine whether LV remodeling is attenuated in patients whose repair is successful long-term. In addition, this study did not address undersizing of rings or the 3-dimensional saddle shape of the mitral annulus. It is possible that use of a ring that better mimics the saddle shape of the annulus may better reduce the distance between papillary muscles and the medial and lateral edges of the annulus.

Summary
Recurrent MR after ring annuloplasty relates to continued LV remodeling. Approaches that also alleviate ventricular remodeling could therefore potentially be part of a more comprehensive and effective management strategy for patients with ischemic MR.

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