Design of a New Surgical Approach for Ventricular Remodeling to Relieve Ischemic Mitral Regurgitation
Insights From 3-Dimensional Echocardiography

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Background—Mechanistic insights from 3D echocardiography (echo) can guide therapy. In particular, ischemic mitral regurgitation (MR) is difficult to repair, often persisting despite annular reduction. We hypothesized that (1) in a chronic infarct model of progressive MR, regurgitation parallels 3D changes in the geometry of mitral leaflet attachments, causing increased leaflet tethering and restricting closure; therefore, (2) MR can be reduced by restoring tethering geometry toward normal, using a new ventricular remodeling approach based on 3D echo findings.

Methods and Results—We studied 10 sheep by 3D echo just after circumflex marginal ligation and 8 weeks later. MR, at first absent, became moderate as the left ventricle (LV) dilated and the papillary muscles shifted posteriorly and mediolaterally, increasing the leaflet tethering distance from papillary muscle tips to the anterior mitral annulus (P<0.0001). To counteract these shifts, the LV was remodeled by plication of the infarct region to reduce myocardial bulging, without muscle excision or cardiopulmonary bypass. Immediately and up to 2 months after plication, MR was reduced to trace-to-mild as tethering distance was decreased (P<0.0001). LV ejection fraction, global LV end-systolic volume, and mitral annular area were relatively unchanged. By multiple regression, the only independent predictor of MR was tethering distance (r²=0.81).

Conclusions—Ischemic MR in this model relates strongly to changes in 3D mitral leaflet attachment geometry. These insights from quantitative 3D echo allowed us to design an effective LV remodeling approach to reduce MR by relieving tethering. (Circulation. 2000;101:2756-2763.)

Key Words: mitral valve • regurgitation • ischemia • echocardiography • surgery

Quantitative analysis of cardiac geometry by 3D echocardiography (echo) can help define mechanisms of disease and thereby improve therapy. In ischemic heart disease, altered geometry has been proposed to underlie mitral regurgitation (MR), a common complication that doubles late mortality.1–5

Ischemic MR typically involves the incomplete mitral leaflet closure (IMLC) pattern, in which apically displaced leaflets fail to close effectively at the annulus (Figure 1).6,7 Competing explanations6–19 include abnormal mitral valve tethering by displaced ischemic papillary muscles (PMs) and by annular dilatation,6,7,12,13 versus global left ventricular (LV) dysfunction per se, decreasing the ventricular force acting to close the leaflets,20,21 particularly when they are abnormally tethered.22 These mechanisms are difficult to separate in patients, in whom altered geometry often accompanies dysfunction; they have therapeutic implications, however: surgery can potentially remedy abnormal tethering directly, but not fixed global dysfunction. Evaluating 3D tethering geometry has been further limited by the 2D nature of standard echo.23 Clinical experience has shown that such MR is difficult to repair1,3,24–31 and often persists despite annular reduction.31 Therefore, the purpose of this study was to design more effective therapy on the basis of mechanistic insights from quantitative 3D echo. We studied a chronic infarct model with known progressive MR14,15 to test the hypothesis that regurgitation parallels 3D changes in the geometry of leaflet attachments that increase tethering and restrict closure and therefore, that these mechanistic observations can help design a strategy for restoring tethering geometry toward normal to reduce or eliminate MR.

Methods
The chronic infarction model of Llaneras et al14,15 offers the opportunity to study the evolution of progressive MR, which is absent at first, in the same animals with stable myocardial dysfunction. The study design repeats 3D echo to evaluate mitral geometry at baseline, with acute infarction and only trace MR,
with chronic infarction and moderate MR, and after relief of PM tethering (Figure 2).

Ten Dorset hybrid sheep (40 to 50 kg) anesthetized with thiopental (0.5 mL/kg), intubated, and ventilated at 15 mL/kg with 2% isoflurane and oxygen and given glycopyrrolate (0.4 mg IV) and prophylactic vancomycin (0.5 g IV), underwent sterile left thoracotomy, with procainamide (15 mg/kg IV) and lidocaine (3 mg/kg IV followed by 2 mg/min) given 10 minutes before coronary ligation. After baseline imaging, the pericardium was opened, and the second and third circumflex obtuse marginal branches were ligated to infarct the inferoposterior wall. Imaging was repeated and the thoracotomy closed.

After 8 weeks, each animal had a second thoracotomy under general anesthesia. Because we observed that MR, absent at first, became moderate as the LV dilated and the PMs shifted posteriorly and medially away from the central anterior mitral annulus in 3 dimensions, we designed a procedure to counteract these shifts, working with an animal physiologist and surgeon (J. Luis Guerrero) (Figure 3). The LV was remodeled by plication of the infarct region with mattress sutures to reduce the evident myocardial bulging and bring the displaced PM tip back toward the anterior mitral annulus, relieving tethering. Neither muscle excision nor cardiopulmonary bypass was required. Monofilament 1-0 polypropylene sutures were inserted from the normal epicardium into the infarcted endocardium parallel to the LV long axis. Special 3D software recorded 36 rotated images automatically at 5° increments with ECG gating (Figure 4). During acquisition, respiration was suspended for the most accurate reconstruction. Images were recorded on videotape and digitally on magneto-optical disks for analysis on a Silicon Graphics workstation.

3D Echo Data Collection
3D echo data were acquired with a 5-MHz epicardial transducer (Hewlett-Packard Sonos 2500) for the highest resolution, scanning the heart through a water bath from the LV apex by a rotating-array probe with the beam aligned through the center of the mitral valve, parallel to the LV long axis. Special 3D software recorded 36 rotated images symmetric in this reference frame19 (see Figure 6, which views 3D PM–Mitral Annulus Relations (plane with least deviation of annular hinge points about it)).39 Using this reference, we correlated development of MR with a series of uniquely 3D measurements that cannot be made in any 2D view. Mitral geometry was analyzed from rotated mid-systolic images (most effective leaflet closure, Figure 5). Displaying intersecting views simultaneously enhanced spatial appreciation (top left). The ventricular borders of the mitral leaflets were traced and the mitral and aortic annuli (top right) identified as the leaflet hinge points, confirmed by video review. The PMs were traced and their tips closest to the cardiac base and anterior annulus determined by review of several adjacent images. An endocardial surface color-coded for adjacent structures (bottom left) was generated,32 and spatial relations of the mitral apparatus were established (bottom right).

The tethering length over which the mitral leaflets and chordae are stretched between the PMs and the relatively fixed fibrous portion of the annulus was then measured19 from each PM tip to the medial trigone of the aortic valve (medial junction of aortic and mitral annuli); this point was selected because the line connecting it with the mitral annular centroid roughly bisected the line connecting the PM tips, so that symmetric outward PM displacements appear symmetric in this reference frame19 (see Figure 6, which views 3D data). Changes in these tethering distances relative to baseline were measured, as well as changes in the PM tip separation.
These 3D echo measurements have correlated and agreed well with distances measured by sonomicrometer crystal array (Sonometrics), both in vivo (4 PM and annular crystals, 2 times per beat, several hemodynamic stages, n=36) and in a ventricular phantom (8 crystals, n=28): y=0.99x+0.2, r²=0.99, SEE=0.7 mm, P<10⁻¹⁰; mean difference=0.08±0.7 mm (not significant versus 0).

Statistical Analysis
LV volumes and ejection fraction (EF), MR volume, and mitral geometric measures were compared among stages and sheep by 2-way ANOVA, with significance at P<0.005 because of the number of variables studied. Significant ANOVAs were explored by 4 paired t tests (acute ligation versus baseline, and chronic ligation versus acute ligation, acute plication, and chronic plication), with significance at P<0.015 (Bonferroni-corrected). MR stroke volume determinants were explored by univariate and stepwise multiple linear regression analysis, entering the absolute value and changes relative to baseline of the 3D measures of mitral attachment geometry (tethering distances for each PM and the sum for both, inter-PM distance and annular area) and LV volumes and EF. Variables were entered as suggested by the regression model F value at P<0.05.

Results
Progression of Ischemic MR: Mechanistic Study
At baseline, the mitral leaflets closed at the annular level without MR by color Doppler (Figure 7A). With acute infarction, LV dilatation was limited (Table), and the leaflets still closed at the annular level, with only trace MR. After 8 weeks of infarction, however, although EF was comparable (38±3% versus 42±2%), LV volumes were considerably higher, and the leaflets remained apically tented with moderate MR (regurgitant volume, 10.5±1.5 versus 0.7±0.3 mL per beat at baseline; regurgitant fraction, 35±13% [19% to 59%]). Figure 7B shows the corresponding 3D geometric changes viewed from the apex. With acute infarction, tethering distance increased only slightly; with chronic LV remodeling, however, the PMs, especially the medial one in the central infarct zone, were considerably displaced away from the anterior annulus as leaflet closure was restricted and MR developed.

Reversal of Ischemic MR: Therapeutic Study
With infarct plication, although EF was unchanged (39±3% versus 38±3%), the leaflets were able to close at the annular level, with only trace MR (Figure 8A). This benefit persisted over the 10 days to 2 months of follow-up (the example is 5 weeks after repair). 3D analysis (Figure 8B) showed correspondingly reduced tethering distances, with similar results in all 10 animals. The excised hearts revealed smooth endocardium throughout the plicated region, without thrombus.
Quantitative Measures

MR volume increased with infarct remodeling and decreased with plication (Figure 9A), with parallel changes in tethering distance (sum for both PMs, $P<0.0001$). MR volume (Figure 9B) varied with changes in tethering distance, plotted as the mean for each stage ($y=0.13x^6+0.7$, $r^2=0.99$, SEE=0.09). In contrast to the prominent changes in MR and tethering distance with plication and its follow-up, there were relatively small and insignificant changes in EF, mitral annular area, and LV volumes (Figure 9C, Table).

Univariate predictors of MR stroke volume were the absolute value and its change from baseline of the tethering lengths of both PMs, the PM tip separation, IMLC area, and LV end-diastolic and end-systolic volumes. MR stroke volume did not correlate with LVEF, mitral annular area, or sheep studied ($P=0.38, 0.11, \text{and } 0.35$). Multiple linear regression analysis identified the change from baseline in the sum of tethering distances as the only independent factor determining MR stroke volume ($r^2=0.81, P=6\times10^{-8}$, SEE=1.3).

Discussion

The results show that ischemic LV contractile dysfunction fails to produce important MR immediately without LV dilatation or distortion. In contrast, MR does develop over

A  Progression of Ischemic MR

Baseline  Acute MI  Chronic MI

B  Change in the Geometry of Mitral Leaflet Attachments in a chronic Model of Ischemic Mitral regurgitation

Baseline  Acute  Chronic

Figure 6. 3D reconstruction viewed from apex. Black arrows indicate projections onto this image plane of PM tip-to-anterior mitral annulus tethering distances to medial trigone (aortic-mitral annular junction), about which PMs lie symmetrically.

Figure 7. A, IMLC and MR progression in mid-systolic apical 4-chamber views (color flow below) from baseline and acute myocardial infarction (MI; leaflets close at annulus with no-trace MR) to chronic myocardial infarction (apically tented leaflets [below] with moderate MR in a dilated LV). B, Corresponding 3D reconstructions: only mild medial PM displacement (green) with acute MI, more prominent chronically.
time at the same EF if the LV remolds and dilates. 3D echo directly confirmed geometric changes associated with such remodeling, including an increased distance over which the mitral leaflets are tethered from the PMs to the anterior annular ring, as well as an increased mitral annular area to be covered. These changes stretch the leaflets wide over the annulus and restrict their ability to close effectively at the annular level, resulting in apical tenting (Figure 1). Most importantly, reversing these changes by plicating the infarct zone to reduce tethering distance reduces or eliminates MR. These benefits notably occurred with only mild decreases in total LV volume, indicating the importance of localized geometric changes affecting the mitral valve attachments as opposed to nonspecific global dilatation. This has significance for therapy, because localized reshaping may be easier to achieve than global LV restructuring.

Mechanistic Considerations
These results highlight the importance of the PM tip-to-annulus distance in determining mitral valve behavior. The steep rise in MR only at relatively large tethering distances (Figure 9B, curvilinear relationship) is what we would expect if increased tethering exhausts the normal surplus leaflet area, causing MR. These benefits notably occurred with only mild decreases in total LV volume, indicating the importance of localized geometric changes affecting the mitral valve attachments as opposed to nonspecific global dilatation. This has significance for therapy, because localized reshaping may be easier to achieve than global LV restructuring.

Methodological Considerations
These measurements demand 3D echo to relate multiple structures in multiple imaging planes and to provide a consistent measurement reference frame, including the least-squares plane of the nonplanar mitral annulus and its medial trigone, about which the PMs lie symmetrically. 3D echo allows us to recognize the most basal tips of the PMs by paging through several adjacent imaging planes, and provides precise, validated LV volumes and EF.

Limitations
The clinical spectrum of ischemic MR includes widely varying location and chronicity of ischemia, PM tip geometry, and potentially leaflet length. Some of this variation, especially the development of chronic changes and LV remodeling, is reflected in this model. The purpose of this study, however, was specifically to explore a model that could separate LV contractile function changes, present in all infarct stages, from major tethering distance changes present in the chronic stage and also to evaluate 3D mitral geometric relations and restore them toward normal. This was achieved with a model of inferoposterior ischemia resembling the pattern seen in many patients with ischemic MR. Plication was applied to akinetic or dyskinetic myocardium. Inferior hypokinesis alone typically produces milder MR and promises greater viability with revascularization; further investigation is necessary to refine approaches to decrease tethering in diffusely hypokinetic hearts, including circumferential reduction by external constraint.

Practical Implications
This quantitative 3D analytic technique has also been extended to clinical studies to show that in patients with inferior infarctions of comparable size and LVEF, PM tethering distance determines MR, as it does in patients undergoing coronary revascularization (N.L.-C., A.H., unpublished data, 1999). These results are consistent with clinical and experimental observations that regional wall motion abnormality can induce functional MR, but they demonstrate that the primary cause of MR is not the LV dysfunction per se but rather the associated geometric changes. This can also be a consideration in decisions regarding potential benefit of thrombolysis in acute inferior infarctions, despite their often limited size.
The present study suggests the possibility that surgical approaches such as LV plication, applied at the time of myocardial revascularization, could potentially benefit patients by restoring overall 3D mitral geometry toward normal. Resecting posterior wall muscle between the PMs in failing ventricles may reduce MR, in part, by moving the PMs closer together to decrease tethering; however, unlike plication, it requires muscle excision and cardiopulmonary bypass. Although ring annuloplasty can limit annular area and improve coaptation, clinical observations suggest that this is not always the case, because PM tethering persists. This has led to combining annuloplasty with PM shortening or reimplantation and infarct exclusion via a transventricular route. PM tethering, however, could also potentially be addressed by the plication technique in this study: it directly targets the fundamental imbalance restricting leaflet closure and aims to overcome the variable, often frustrating results seen with various annuloplasty and other techniques requiring cardiopulmonary bypass. Plication in principle also preserves chordal continuity to maintain LV function as a benefit of valve repair versus replacement.

Conclusions

Ischemic MR in this chronic infarct model relates strongly to changes in the 3D geometry of valve attachments; more favorable tethering reduces MR and can be achieved by LV remodeling surgery developed on the basis of the 3D echo findings.

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Figure 9. A, Parallel changes in MR volume and tethering distance. MI indicates myocardial infarction. B, MR volume vs change from baseline in tethering distance (sum for both PMs), with means and SEMs for each stage. C, Changes in MR volume, mitral annular area, LV EF, and LV end-systolic volume (LVESV) by stage (1, baseline; 2, acute infarction; 3, chronic infarction; 4, plication; and 5, recovery).

References
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