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 (r^2 =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 explanations^{6–19} 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 repair^{1,3,24–31} 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 MR^{14,15} 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 al^{14,15} 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,

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Figure 1. Left, Mitral balance of forces. AO indicates aorta; LA, left atrium; and dashed line, annulus. Right, Potential effect of PM displacement to restrain leaflet closure, causing 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 thiopentothal (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 mediolaterally 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 and back out to the normal zone on both medial and lateral infarct margins, taking care to avoid incorporating coronary artery branches. These 2 rows of sutures parallel to the LV long axis were in turn linked by mattress sutures to reduce the proportion of the LV circumference occupied by the infarcted myocardium. Because circumference is proportional to diameter, reducing posterior wall circumference also reduces its anteroposterior diameter or distance to the anterior wall. Plication therefore brings the posteriorly located PMs closer to the relatively fixed anterior mitral annulus. This procedure was guided by manual compression of the infarcted region to see how much reduction in bulging would eliminate MR, which was imaged simultaneously by color Doppler from the apex. Appearance, shape, and motion of the akinetic or dyskinetic infarct zone provided external guiding landmarks. After sterile closure and observation for 10 days to 2 months, thoracotomy was repeated under general anesthesia for imaging, and euthanasia was induced with thiopentothal and potassium chloride.



Figure 2. Study design.



Figure 3. LV remodeling (infarct plication) to bring displaced PM tip back toward anterior annulus, reducing MR. LA indicates left atrium; AO, aorta.

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 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.

Data Analysis

LV end-diastolic and end-systolic volumes were obtained by 3D echo using endocardial borders from 6 rotated views and a validated surfacing algorithm.³² Mitral regurgitant stroke volume was calculated as LV ejection volume minus aortic outflow volume³³ (the time-velocity integral of forward flow times annular area).³⁴ The IMLC apical tenting area was measured between leaflets and annulus in the apical 4-chamber view at mid systole (closest leaflet-annulus approach).^{7,35}

3D PM–Mitral Annulus Relations

We aimed to identify PM displacement relative to the annulus, increasing tethering and potentially impairing coaptation.^{17,36–38} As reference frame we took the least-squares plane of the mitral annulus (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 relations from the apex with the annulus en face). Changes in these tethering distances relative to baseline were measured, as well as changes in the PM tip separation.





Figure 4. 3D echo rotatingprobe acquisition of apical images, shown intersecting endocardial surface (color).

These 3D echo measurements have correlated and agreed well with distances measured by sonomicrometer crystal array (Sonometrics),^{14–16} 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+02, $r^2=0.99$, 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 (tehering 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 $(38\pm3\%)$ versus $42\pm2\%$, 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, $35\pm13\%$ [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 $(39\pm3\% \text{ versus } 38\pm3\%)$, 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.



Figure 5. 3D reconstruction. Top left, Two intersecting images, 1 through each PM. Top right, Points traced to identify endocardium (red), PM indentation (orange), PM tips (yellow, blue), and mitral leaflets (green). Bottom left, Colormapped LV surface (mitral annulus, blue; outflow tract, purple). Bottom right, Extracting PM spatial relations to mitral annulus, including distances to anterior annulus (red). Mitral annulus is a thin 3D curve (light gray, leastsquares plane; centroid, white; aortic annulus, brown; and centroid, blue).

Tethering Distances Between Papillary Muscles and Anterior Mitral Annulus



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.

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

^A Progression of Ischemic MR



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



9B) varied with changes in tethering distance, plotted as the mean for each stage ($y=0.13x^{1.6}+0.7$, $r^2=0.99$, 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, 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

> **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

> B, Corresponding 3D reconstructions: only mild medial PM displacement (green) with acute MI, more prominent chronically.

LV and Mitral Indices Among Stages

	Baseline	Coronary Ligation: Acute	Coronary Ligation: Chronic	Plication: Acute	Plication: Chronic
LVEDV, mL	38.7±2.7	45.5±3.5*	78.4±5.7†	69.1±5.0	71.6±6.1
LVESV, mL	19.5±1.6	26.2±2.1*	48.7±4.6†	42.2±3.9	46.6±4.3
LVEF, %	50±2	42±2*	38±3	39±3	35±3
LV ejection volume, mL	19.2±1.6	19.3±1.9	29.8±2.5†	26.9±2.6	25.0±3.2§
Aortic stroke volume, mL	18.9±1.6	18.4±2.1	19.3±2.0	24.8±2.8	23.4±2.8
MR volume, mL/beat	$0.7 {\pm} 0.3$	1.3±0.5*	10.5±1.5†	2.1±0.3‡	2.1±0.4§
IMLC area, cm ²	$0.04 {\pm} 0.05$	$0.08 {\pm} 0.05$	0.63±0.13†	$0.20 \pm 0.04 \ddagger$	$0.30 {\pm} 0.04 \$$
PM-MA, mm					
Medial	23.2±0.4	25.0±0.8	32.9±1.5†	26.3±0.7‡	25.8±0.7§
Lateral	27.5±0.6	27.8±0.7	33.0±1.0†	28.7±1.2‡	29.3±0.8§
Sum	50.7±0.7	52.8±1.2	65.9±2.4†	55.1±1.4‡	55.1±1.4§
D, mm	19.7±1.2	25.0±1.2*	31.3±1.4†	26.4±1.5‡	26.7±1.1§
MA area, cm ²	$6.1{\pm}0.3$	6.3±0.4	7.3±0.4†	6.9±0.3	7.0±0.2

LVEDV indicates LV end-diastolic volume; LVESV, LV end-systolic volume; PM-MA, distance of PM from mitral annulus (MA); and D, distance between PMs.

All 2-way ANOVAs for individual variables were significant at P<0.0001, except mitral annular area (P<0.002) and aortic stroke volume (P<0.02). Significant changes (P<0.0125, Bonferroni) are indicated for the 2-way comparisons: *acute ligation relative to baseline, †chronic ligation relative to acute ligation, ‡acute plication relative to chronic ligation and §chronic plication relative to chronic ligation.

time at the same EF if the LV remodels 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-toannulus distance in determining mitral valve behavior.¹⁷ 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.^{3,37,38}

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^{39–42} 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.³²

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.19

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., Y.O., 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.^{12–19} This can also be a consideration in decisions regarding potential benefit of thrombolysis in acute inferior infarctions, despite their often limited size.⁴³

Reversal of Ischemic MR

Α



Figure 8. A, IMLC and MR reversal, from moderate to trace with leaflets closing more superiorly at annular level with plication and 5 weeks later. MI indicates myocardial infarction. B, Corresponding 3D reconstructions from apex: plication decreases PM tethering distances.

B Change in the Geometry of Mitral Leaflet Attachments with Reversal of Ischemic Mitral Regurgitation



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.44 Resecting posterior wall muscle between the PMs in failing ventricles may reduce MR, in part, by moving the PMs closer together to decrease tethering⁴⁵; 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,³¹ because PM tethering persists^{16,18}; this has led to combining annuloplasty with PM shortening or reimplantation and infarct exclusion via a transventricular route.^{1,3} 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.^{1,3,24-31} Plication in principle also

preserves chordal continuity to maintain LV function⁴⁶ 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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MR Volumes and Changes in Tethering Distance



1-Base 2-Acute MI 3-Chronic MI 4-Plication 5-Recovery





Changes in MR, LVEF, Annular Area and LVESV



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, LVEF, and LV end-systolic volume (LVESV) by stage (1, baseline; 2, acute infarction; 3, chronic infarction; 4, plication; and 5, recovery).

References

- Rankin JS, Hickey MSJ, Smith LR, et al. Ischemic mitral regurgitation. *Circulation*. 1989;79(suppl I):I-116–I-121.
- Fleischmann KE, Goldman L, Robiolio PA, et al. Echocardiographic correlates of survival in patients with chest pain. J Am Coll Cardiol. 1994;23:1390–1396.
- Frater RWM, Cornelissen P, Sisto D. Mechanisms of ischemic mitral insufficiency and their surgical correction. In: Vetter HO, Hetzer R, Schmutzler H, eds. *Ischemic Mitral Incompetence*. New York, NY: Springer-Verlag; 1991:117–130.

- Barzilai B, Gessler C Jr, Perez JE, et al. Significance of Doppler-detected mitral regurgitation in acute myocardial infarction. *Am J Cardiol.* 1988; 61:220–223.
- Lehmann KG, Francis CK, Dodge HT, and the TIMI Study Group. Mitral regurgitation in early myocardial infarction: incidence, clinical detection, and prognostic implications. *Ann Intern Med.* 1992;117:10–17.
- Ogawa S, Hubbard FE, Mardelli TJ, et al. Cross-sectional echocardiographic spectrum of papillary muscle dysfunction. *Am Heart J*. 1979;97: 312–321.
- Godley RW, Wann LS, Rogers EW, et al. Incomplete mitral leaflet closure in patients with papillary muscle dysfunction. *Circulation*. 1981; 63:565–571.
- Burch GE, De Pasquale NP, Phillips JH. Clinical manifestations of papillary muscle dysfunction. Arch Intern Med. 1963;59:508–520.
- Mittal AK, Langston M Jr, Cohn KE, et al. Combined papillary muscle and left ventricular wall dysfunction as a cause of mitral regurgitation: an experimental study. *Circulation*. 1971;44:174–180.
- Izumi S, Miyatake K, Beppu S, et al. Mechanism of mitral regurgitation in patients with myocardial infarction: a study using real-time twodimensional Doppler flow imaging and echocardiography. *Circulation*. 1987;76:777–785.
- Kisanuki A, Otsuji Y, Kuroiwa R, et al. Two-dimensional echocardiographic assessment of papillary muscle contractility in patients with prior myocardial infarction. J Am Coll Cardiol. 1993;21:932–938.
- Kono T, Sabbah HN, Rosman H, et al. Mechanism of functional mitral regurgitation during acute myocardial ischemia. J Am Coll Cardiol. 1992;19:1101–1105.
- Sabbah HN, Kono T, Rosman H, et al. Left ventricular shape: a factor in the etiology of functional mitral regurgitation in heart failure. *Am Heart J*. 1992;123:961–966.
- Llaneras MR, Nance ML, Streicher JT, et al. Pathogenesis of ischemic mitral insufficiency. J Thorac Cardiovasc Surg. 1993;105:439–443.
- Llaneras MR, Nance ML, Streicher JT, et al. Large animal model of ischemic mitral regurgitation. *Ann Thorac Surg.* 1994;57:432–439.
- Gorman RC, McCaughan JS, Ratcliffe MB, et al. Pathogenesis of acute ischemic mitral regurgitation in three dimensions. *J Thorac Cardiovasc* Surg. 1995;109:684–693.
- Komeda M, Glasson JR, Bolger AF, et al. Geometric determinants of ischemic mitral regurgitation. *Circulation*. 1997;96(suppl II):II-128–II-133.
- Komeda M, Glasson JR, Bolger AF, et al. Papillary muscle-left ventricular wall "complex." J Thorac Cardiovasc Surg. 1997;113:292–300.
- Otsuji Y, Handschumacher MD, Schwammenthal E, et al. Insights from three-dimensional echocardiography into the mechanism of functional mitral regurgitation: direct in vivo demonstration of altered leaflet tethering geometry. *Circulation*. 1997;96:1999–2008.
- Kaul S, Spotnitz WD, Glasheen WP, et al. Mechanism of ischemic mitral regurgitation: an experimental evaluation. *Circulation*. 1991;84: 2167–2180.
- Dent JM, Spotnitz WD, Nolan SP, et al. Mechanism of mitral leaflet excursion. Am J Physiol. 1995;269:H2100–H2108.
- He S, Fontaine AA, Schwammenthal E, et al. Integrated mechanism for functional mitral regurgitation: leaflet restriction versus coapting force: in vitro studies. *Circulation*. 1997;96:1826–1834.
- Boltwood CM, Tei C, Wong M, et al. Quantitative echocardiography of the mitral complex in dilated cardiomyopathy: the mechanism of functional mitral regurgitation. *Circulation*. 1983;68:498–508.
- Carpentier A, Chauvaud S, Fabiani JN, et al. Reconstructive surgery of mitral valve incompetence: ten-year appraisal. *J Thorac Cardiovasc Surg.* 1980;79:338–348.
- David TE. Techniques and results of mitral valve repair for ischemic mitral regurgitation. *Card Surg.* 1994;9(suppl):274–277.
- Arcidi JM Jr, Hebeler RF, Craver JM, et al. Treatment of moderate mitral regurgitation and coronary disease by coronary bypass alone. J Thorac Cardiovasc Surg. 1988;95:951–959.
- Hendren WG, Nemec JJ, Lytle BW, et al. Mitral valve repair for ischemic mitral insufficiency. Ann Thorac Surg. 1991;52:1246–1252.
- Akins CW, Hilgenberg AD, Buckley MJ, et al. Mitral valve reconstruction versus replacement for degenerative or ischemic mitral regurgitation. *Ann Thorac Surg.* 1994;58:668–675.
- Cohn LH, Rizzo RJ, Adams DH, et al. The effect of pathophysiology on the surgical treatment of ischemic mitral regurgitation: operative and late risks of repair versus replacement. *Eur J Cardiothorac Surg.* 1995;9: 568–574.

- Connolly MW, Gelbfish JS, Jacobowitz IJ, et al. Surgical results for mitral regurgitation from coronary artery disease. J Thorac Cardiovasc Surg. 1986;91:379–388.
- Liel-Cohen N, Otsuji Y, Vlahakes GJ, et al. Functional ischemic mitral regurgitation can persist despite ring annuloplasty: mechanistic insights. *Circulation*. 1997;96(suppl I):I-540. Abstract.
- Handschumacher MD, Lethor J-P, Siu SC, et al. A new integrated system for three-dimensional echocardiographic reconstruction: development and validation for ventricular volume with application in human subjects. *J Am Coll Cardiol*. 1993;21:743–753.
- Blumlein S, Bouchard A, Schiller NB, et al. Quantification of mitral regurgitation by Doppler echocardiography. *Circulation*. 1986;74: 306–314.
- Magnin PA, Stewart JA, Myers S, et al. Combined Doppler and phased-array echocardiographic estimation of cardiac output. *Circulation*. 1981;63:388–392.
- 35. Schwammenthal E, Chen C, Benning F, et al. Dynamics of mitral regurgitant flow and orifice area in different forms of mitral regurgitation: physiologic application of the proximal flow convergence method. *Circulation*. 1994;90:307–322.
- Burch GE, De Pasquale NP, Phillips JH. The syndrome of papillary muscle dysfunction. Am Heart J. 1968;75:399–415.
- Levy MJ, Edwards JE. Anatomy of mitral insufficiency. Prog Cardiovasc Dis. 1962;5:119–144.
- Perloff JD, Roberts WC. The mitral apparatus: functional anatomy of mitral regurgitation. *Circulation*. 1972;46:227–239.
- 39. Levine RA, Handschumacher MD, Sanfilippo AJ, et al. Threedimensional echocardiographic reconstruction of the mitral valve, with

implications for the diagnosis of mitral valve prolapse. *Circulation*. 1989; 80:589–598.

- Gorman JH III, Gorman RC, Jackson BM, et al. Distortions of the mitral valve in acute ischemic mitral regurgitation. *Ann Thorac Surg.* 1997;64: 1026–1031.
- Pai RG, Tanimoto M, Jintapakom W, et al. Volume-rendered threedimensional dynamic anatomy of the mitral annulus using a transesophageal echocardiographic technique. J Heart Valve Dis. 1995;4: 623–627.
- 42. Yamaura Y, Yoshikawa J, Yoshida K, et al. Three-dimensional analysis of configuration and dynamics in patients with an annuloplasty ring by multiplane transesophageal echocardiography: comparison between flexible and rigid annuloplasty rings. *J Heart Valve Dis.* 1995;4: 618–622.
- 43. Tenenbaum A, Leor J, Motro M, et al. Improved posterobasal segment function after thrombolysis is associated with decreased incidence of significant mitral regurgitation in a first inferior myocardial infarction. *J Am Coll Cardiol*. 1995;25:1558–1563.
- Bolling SF, Deeb GM, Brunsting LA, et al. Early outcome of mitral valve reconstruction in patients with end-stage cardiomyopathy. *J Thorac Cardiovasc Surg.* 1995;4:676–683.
- Batista RJV, Santos JLV, Takeshita N, et al. Partial left ventriculectomy to improve left ventricular function in end-stage heart disease. J Card Surg. 1996;11:96–97.
- David TE, Ho WC. The effect of preservation of chordae tendineae on mitral valve replacement for postinfarction mitral regurgitation. *Circulation*. 1986;74(suppl I):I-116–I-120.