

# Reverse Ventricular Remodeling Reduces Ischemic Mitral Regurgitation

## Echo-Guided Device Application in the Beating Heart

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**Background**—In ischemic mitral regurgitation (MR), mitral leaflet closure is restricted by ventricular remodeling with displacement of the papillary muscles (PMs). Therapy is uncertain because ring annuloplasty does not alleviate PM displacement. We tested the hypothesis that echo-guided PM repositioning using an external device can reduce MR without compromising left ventricular (LV) function.

**Methods and Results**—We studied 10 sheep with ischemic MR produced by circumflex ligation with inferior infarction, 6 acutely and 4 eight weeks after myocardial infarction (MI). A Dacron patch containing an inflatable balloon was placed over the PMs and adjusted under echo guidance to reverse LV remodeling and reposition the infarcted PM. 3D echo assessed mitral valve geometric changes. In 7 sheep, sonomicrometry and Millar catheters assessed changes in end-systolic and end-diastolic pressure-volume relationships, and microspheres were injected to assess coronary flow. Moderate MR after MI resolved with patch application alone (n=3) or echo-guided balloon inflation, which repositioned the infarcted PM, decreasing the PM tethering distance from  $31.1 \pm 2.5$  mm after MI to  $26.8 \pm 1.8$  with patch ( $P < 0.01$ ; baseline =  $25.5 \pm 1.5$ ). LV contractility was unchanged (end-systolic slope =  $3.4 \pm 1.6$  mm Hg/mL with patch versus  $2.8 \pm 1.6$  after MI). Although there was a nonsignificant trend for a mild increase in stiffness constant ( $0.07 \pm 0.05$  mL<sup>-1</sup> versus  $0.05 \pm 0.03$  after MI,  $P = 0.06$ ), LV end-diastolic pressure was unchanged as MR resolved. Coronary flow to noninfarcted regions was not reduced.

**Conclusions**—An external device that repositions the PMs can reduce ischemic MR without compromising LV function. This relatively simple technique can be applied under echo guidance in the beating heart. (*Circulation*. 2002;106:2594-2600.)

**Key Words:** ischemia ■ mitral valve ■ ventricles ■ regurgitation ■ echocardiography

Beyond its diagnostic role, echocardiography is gaining recognition as an important participant in the therapeutic process. It allows us to design specifically targeted therapy based on an understanding of mechanism and also to devise less invasive therapy because it can monitor therapeutic end points in the beating heart. Echo guidance, for example, now plays a role in percutaneous shunt closure and alcohol interventricular septal ablation.<sup>1,2</sup> Our goal was to extend this new role of echocardiography to the treatment of ischemic mitral regurgitation (MR).

Ischemic MR is a common complication of coronary artery disease that doubles late mortality.<sup>3,4</sup> Extensive evidence has shown that ischemic MR results from left ventricular (LV) distortion, which displaces the papillary muscles (PMs) and tethers the mitral leaflets apically, restricting their closure.<sup>5-12</sup> Therapy for ischemic MR, however, remains problematic.

Mitral ring annuloplasty, often applied at the time of bypass surgery, reduces mitral annular size but does not directly address the broader problem of ischemic LV distortion with tethering; its benefits are therefore incomplete, particularly when LV remodeling continues to progress postoperatively.<sup>13,14</sup> Uncertain benefit and the need for atrial incision and cardiopulmonary bypass can deter surgical repair.

Our hypothesis was therefore that repositioning the PMs using an external device can reduce ischemic MR. The approach uses a Dacron patch containing an inflatable balloon placed over the PMs. This was tested in an experimental model of ischemic MR produced by inferior infarction. The proposal was that placing the patch and, if necessary, inflating the balloon locally can potentially reverse LV remodeling and reposition the infarcted PM toward the anterior mitral annulus, thereby reducing leaflet tethering and MR (Figure

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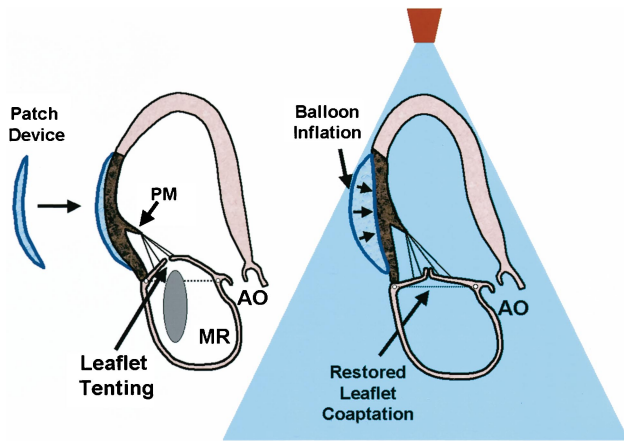
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**Figure 1.** Patch placement and balloon inflation over the infarct region (highlighted) repositions the displaced PM toward the anterior annulus to relieve tethering and MR, monitored by ultrasound. Ao indicates aorta.

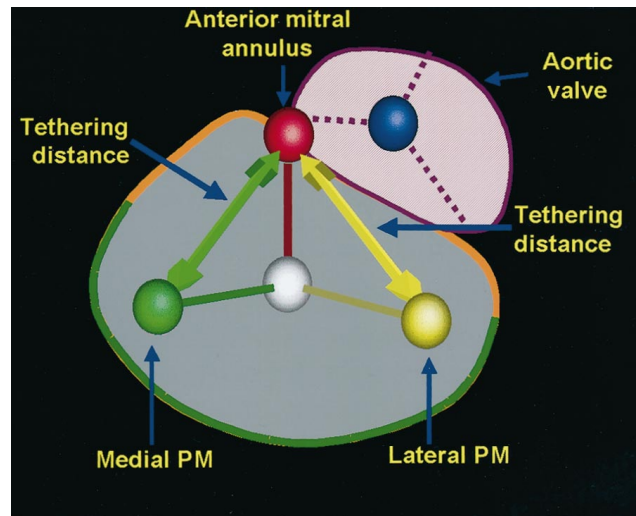
1). This approach directly targets tethering and has the potential to be individually titrated under echocardiographic guidance in the beating heart.

## Methods

A total of 10 Dorset hybrid sheep (30 to 40 kg) were anesthetized with thiopentothal sodium (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), with procainamide (15 mg/kg IV) and lidocaine (3 mg/kg IV) followed by 2 mg/min) infused 10 minutes before coronary ligation. A surface ECG was monitored and a sterile left thoracotomy performed with pericardial incision. A high-fidelity micro-manometer-tipped catheter (Millar Instruments) was placed into the LV via the carotid artery. In 6 sheep, after baseline hemodynamics and echocardiographic imaging (see below), acute MR was produced by ligating the second and third obtuse marginal branches of the left circumflex coronary artery as well as its continuation into the posterior descending artery at their origins.<sup>15,16</sup> Echo imaging monitored the development of MR over 30 to 60 minutes, after which hemodynamic measurements and echo imaging were repeated. PM repositioning was then attempted (see below) and measurements repeated. In 4 additional sheep, the chronic ischemic MR model of Llaneras and Edmunds was used, which produces MR only with LV remodeling over 8 weeks.<sup>15,16</sup> Circumflex obtuse marginals 2 and 3 were ligated. After hemodynamic and echo measurements, the thoracotomy was closed and the animals were cared for over 8 weeks. A second thoracotomy was then performed for imaging and PM repositioning. In both acute and chronic models, pressure-volume loop ventricular function studies with implanted crystals were performed before and after patch device placement during the same thoracotomy.

## PM Repositioning

The patch-balloon device was sewn onto the myocardium over the region of infarction (visible by alterations in color and bulging motion pattern) using interrupted sutures, taking care to avoid occluding epicardial coronary arteries. An elongated oval balloon (parallel to the LV long axis) was contained between the patch and the myocardium (Figure 1). This arrangement of the Dacron patch sewn over the balloon buttresses the balloon so that during inflation, the displacement of the myocardium is exclusively inward toward the anterior mitral annulus. Patch placement and degree of balloon inflation were guided in situ by echocardiography to achieve reduction of MR with normal seating of the leaflets using a minimum amount of fluid injected (0 to 15 mL, in 2- to 5-mL increments, Figure 1). This also permitted immediate adjustment of the device if



**Figure 2.** 3D mitral valve geometry viewed from the apex, showing the PM tips (yellow and green), posterior mitral annulus (green curve), anterior annulus (orange curve, red trigone), mitral annular centroid (white), and aorta (purple).

necessary. With the device properly positioned, echocardiographic and hemodynamic measurements were repeated.

## Data Collection and Analysis

LV pressure was recorded along with an ECG lead on a multichannel physiological recorder. 2D, Doppler, and 3D echo data were collected using a high-frequency (3.5 to 5 MHz) transesophageal multiplane probe imaging the heart through a water bath. For 3D reconstruction, the probe was positioned to align the axis of rotation from the LV apex through the center of the mitral valve. The probe was interfaced with a Hewlett-Packard Sonos 5500 sector scanner with 3D software to record rotated images at angular increments of 4 degrees. ECG gating was used to record a full cardiac cycle in these 45 rotated planes, with respiration suspended during data acquisition for most accurate reconstruction. Digital images were analyzed on a Silicon Graphics workstation.

## LV Measures

LV end-diastolic and end-systolic volumes were obtained by 3D echo, using endocardial borders from 6 planes at equal angular intervals and a validated surfacing algorithm.<sup>17</sup> Device application was adjusted to reduce MR based on visual assessment of the proximal jet width.<sup>18</sup> MR volume was calculated as the difference between LV ejection volume by 3D echo and forward aortic stroke volume.<sup>19</sup> Regurgitant fraction was calculated as MR stroke volume/total LV ejection volume.

## 3D Analysis of the Mitral Valve Complex

For each echo image, the PM tips, mitral leaflets, mitral annulus, and aortic annulus were traced in mid-systole, with the closest approach of the leaflets to the annulus.<sup>6,8,20</sup> The tethering length over which the mitral leaflets and chordae are stretched between the PMs and the relatively fixed anterior annulus was measured from each PM tip to the medial trigone of the aortic valve (medial junction of aortic and mitral annuli), about which the PM tips are normally symmetric.<sup>8</sup> Tethering length was used because it most strongly predicted ischemic MR in previous studies.<sup>8</sup> Figure 2 summarizes these 3D relations in a single picture with the mitral annulus viewed en face from the apex. 3D echo was used to relate multiple structures in multiple imaging planes, establish the reference frame (annulus and trigone), and optimize selection of the most basal PM tips. These 3D measurements have correlated and agreed well with sonomicrometer crystal data ( $y=0.99x+0.02$ ,  $r^2=0.99$ ,  $SEE=0.7$  mm, mean difference= $0.08\pm 0.7$  mm, NS versus 0).<sup>8,21</sup> Midsystolic mitral annular

**Hemodynamic and Mitral Measures and Ventricular Function and Filling Pressure**

	Baseline	After MI	Patch	ANOVA <i>P</i> Value
HR, bpm	113±6	112±13	121±16	NS
Ao SV, mL	22.4±5.0	21.4±4.9	22.8±5.6	NS
LVSP, mm Hg	84±9	89±16	79±12	NS
EDV, mL	44.9±6.57	63.5±15.9*	54.0±11.9	<0.001
ESV, mL	21.8±5.1	36.1±10.8*	30.3±7.1	<0.001
LVEF	0.52±0.08	0.44±0.08*	0.44±0.05	0.03
MR volume, mL/beat	0.1±1.3	7.8±3.1*	0.9±0.8†	<0.001
MAA, cm <sup>2</sup>	5.3±0.4	6.2±0.6*	6.0±0.5	0.01
PM tethering, mm				
Medial	25.5±1.5	31.1±2.5*	26.8±1.8†	<0.001
Lateral	24.7±2.6	26.1±2.9	25.6±2.2	NS
E <sub>max</sub> , mm Hg/mL	...	2.82±1.60	3.44±1.60	NS
Stiffness constant, mL <sup>-1</sup>	...	0.05±0.03	0.07±0.05	0.06
Coronary blood flow, noninfarct, mL/min per gram	...	0.88±0.28	0.86±0.31	NS
LVEDP, mm Hg	...	12.6±4.4	11.6±6.8	NS

HR indicates heart rate; Ao SV, aortic stroke volume; LVSP, LV systolic pressure; EDV, end-diastolic volume; ESV, end-systolic volume; LVEF, LV ejection fraction; MAA, mitral annular area; PM tethering, tethering distance of each PM to mitral annulus; E<sub>max</sub>, slope of end-systolic pressure-volume relationship; and LVEDP, LV end-diastolic pressure.

\*After MI relative to baseline, *P*<0.001.

†Patch relative to after MI, *P*<0.001.

area was measured as the projection of the annulus on its central plane.<sup>22</sup>

### Measures of LV Contractile Function and Filling

In 7 sheep, LV volumes and contractile performance were assessed using 4 sonomicrometer crystals (Sonometrics) placed over the LV epicardium at base and apex (long axis) and the anterior and posterior walls (short axis). Pressure-volume loops were constructed from continuous tracings of LV volume, calculated using a standard algorithm and Millar micromanometer pressure. The end-systolic pressure-volume relationship as a relatively load-independent measure of LV contractility was obtained by transiently occluding the inferior vena cava with umbilical tape, thereby rapidly producing beats with varying systolic pressures and LV volumes. End-systole was defined as the maximum ratio of LV pressure (LVP) to LV volume, and the end-systolic points were fitted to a linear equation; its slope was taken as a measure of contractile state.<sup>23</sup> End-diastole was defined by the trough in the LVP tracing after atrial contraction. The end-diastolic pressure-volume relationship data from caval occlusion were fitted to the exponential equation  $LVP = A_0 + Be^{Cx}$ , where  $A_0$  is the intercept of the LVP value,  $B$  and  $C$  are curve-fitting parameters,  $x$  is the LV volume, and  $C$  is the stiffness constant.<sup>24</sup>

Echo images were reviewed for any new wall motion abnormalities after device placement. Regional myocardial blood flow in noninfarcted anteroseptal areas (1-g wedges) was measured after myocardial infarction (MI) before and after patch insertion using radiolabeled microspheres injected rapidly into the left atrium after mechanical agitation and flushed with 5 mL of saline, with reference arterial blood samples taken at 2 mL/min.<sup>25</sup>

### Statistical Analysis

The efficacy of the patch-balloon device was tested by 2-way ANOVA of MR volume (baseline, MI without patch, and MI with patch). Significant differences were examined by paired *t* test, using Fisher's *F*-test criterion for multiple comparisons. Other hemodynamic and mitral valve geometric measures were compared among stages and sheep by ANOVA. MR stroke volume determinants were explored by stepwise multiple linear regression analysis, entering LV

volumes and ejection fraction, tethering distances for each PM and their changes, and mitral annular area. Variables were entered as suggested by the regression model *F* value at *P*<0.05.



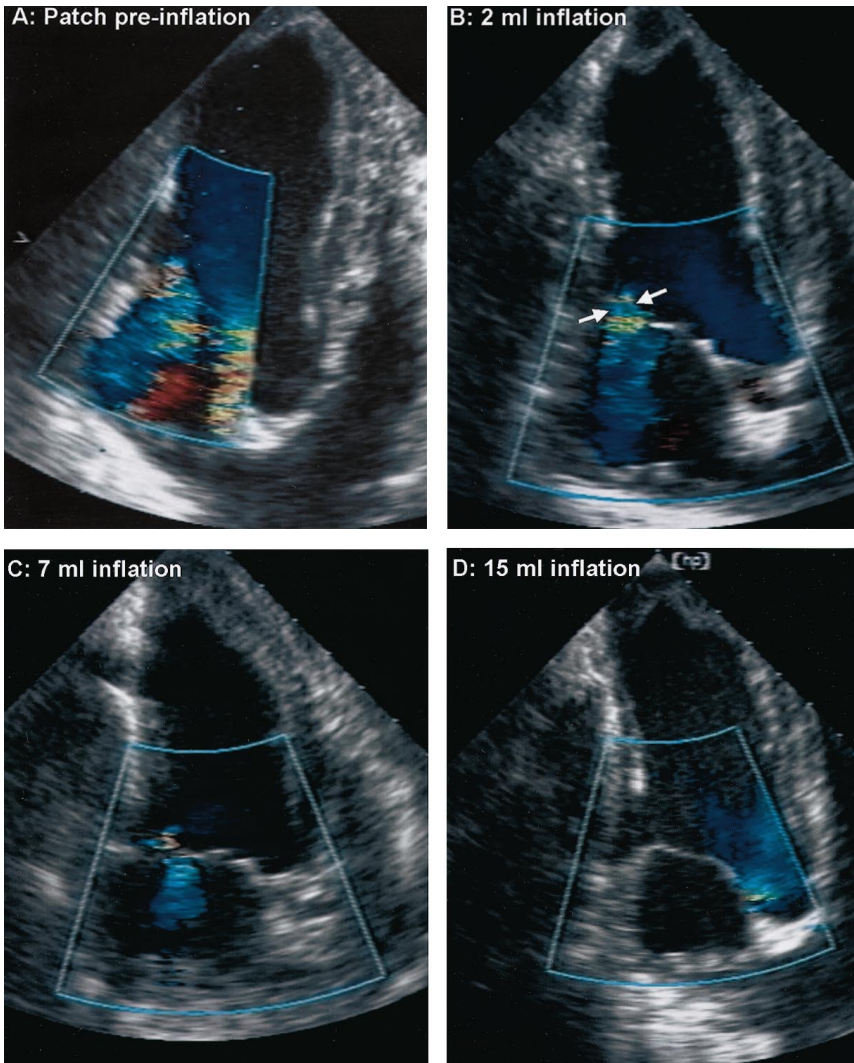
## Results

### Development of MR

All 10 sheep developed MR (depending on the model, acutely or 8 weeks after infarction), with an increase in regurgitant volume from 0.1±1.3 to 7.8±3.1 mL/beat (*P*<0.001, Table) with a mean regurgitant fraction to 27±8%. With infarction and MR, LV ejection fraction decreased significantly, whereas LV end-diastolic and end-systolic volumes increased. The development of MR was associated with increased tethering distance from the inferior PM in the infarcted region to the annulus (25.5±1.5 to 31.1±2.5 mm, *P*<0.001).

### Reduction in MR

Placement of the patch alone substantially reduced MR in 3 sheep (2 chronic and 1 acute); in the other 7, incremental injection of a total of 5 to 15 mL of saline into the balloon, guided by echo imaging, achieved this benefit (overall, 11±4 mL of saline was injected). Figure 3 shows changes in MR with progressive balloon inflation in a sheep with moderate MR 8 weeks after infarction (top left), with little change at 2 mL inflation, a noticeably smaller jet at 7 mL, and no MR at 15 mL. Figure 4 shows how the patch reverses the outward bulging of the remodeled infarcted wall. The corresponding changes in mitral valve geometry are shown in Figure 5. Before patch, the PM is displaced away from the mitral annulus, straightening the anterior leaflet into a hockey stick configuration that limits leaflet tip coaptation.



**Figure 3.** A through D, Changes in MR (proximal jet and jet area in the atrium) with progressive balloon inflation 8 weeks after infarction. Arrows in B indicate proximal jet width.

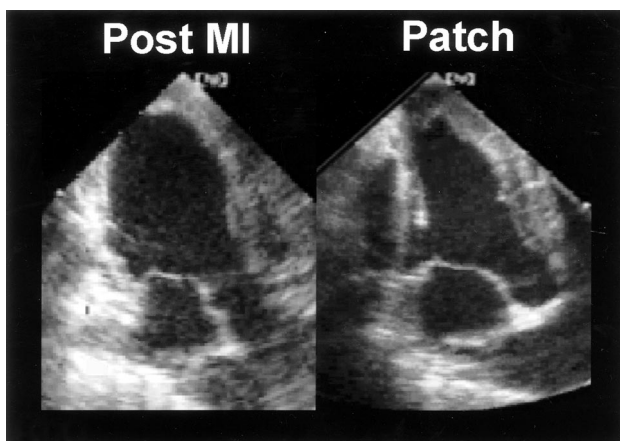


With balloon inflation (right), the PM is shifted anteriorly, and the bend in the anterior leaflet is reduced, with improved leaflet coaptation.

The Movie (available in the online Data Supplement at <http://www.circulationaha.org>) shows how echocardiography

can image the decrease in MR continuously as the patch is gradually inflated with saline.

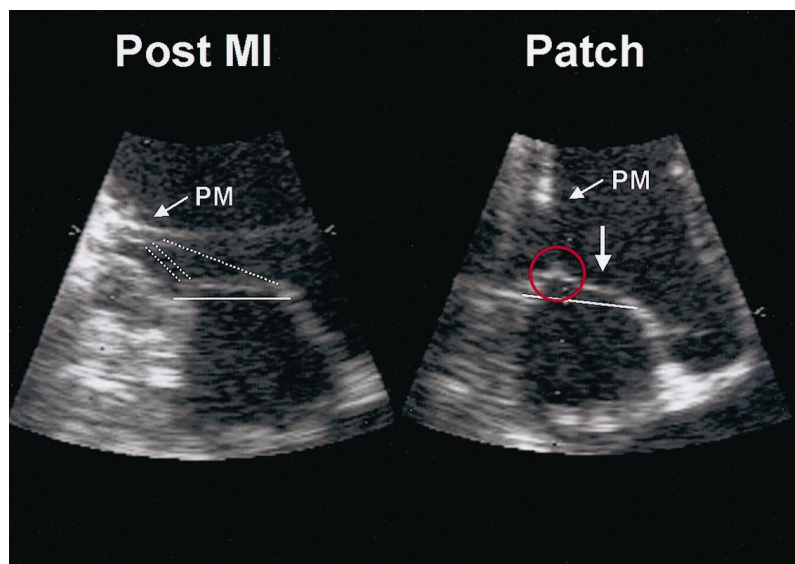
Quantitatively, MR volume decreased to  $0.9 \pm 0.8$  mL/beat ( $P < 0.001$ ) with patch placement (Table), paralleling changes in the tethering distance of the infarcted PM. Figure 6 illustrates the shift in the infarcted PM tip relative to the anterior annulus with infarction and normalization of its position with patch placement. Multiple regression analysis showed that the best model for MR ( $r^2 = 0.64$ ) included changes in the infarcted PM tethering distance, the strongest predictor ( $r^2 = 0.53$ ), with a minor contribution from LV end-diastolic volume.



**Figure 4.** Patch reversal of infarct bulging and remodeling.

**Ventricular Function**

The slope of the LV end-systolic pressure-volume relationship as a measure of LV contractility did not decrease from the infarct stage to that with infarct and patch (Figure 7, Table), with mild increase at lower volumes in several sheep. The end-diastolic pressure-volume curves were variably affected, consistent with the variable balloon inflation needed to reduce MR. There was a nonsignificant trend for a mild increase in stiffness constant (borderline at  $P = 0.06$ ; Table). Nevertheless, after patching and with decreased MR, the



**Figure 5.** Left, Before patch, PM displacement away from the annulus pulls on the mitral leaflets, creating the hockey-stick anterior leaflet configuration that limits leaflet tip coaptation. Right, Balloon inflation shifts the PM anteriorly, reducing the anterior leaflet bend to improve coaptation.

operating point of the LV was shifted to lower volumes (Table), so that LV end-diastolic pressure was not increased relative to the infarct stage ( $11.6 \pm 6.8$  mm Hg with patch versus  $12.6 \pm 4.4$  mm Hg before patch,  $P=NS$ ). Echo imaging showed no new areas of wall motion abnormality after patch placement, and coronary blood flow to the noninfarcted anterior and septal walls was not reduced (Table).

### Discussion

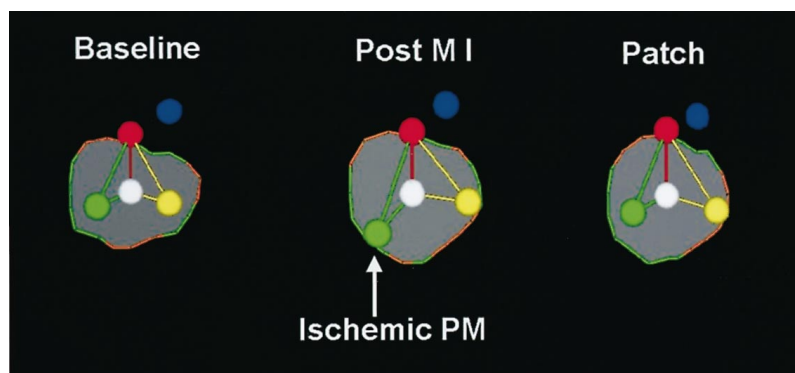
Despite the clinical importance of ischemic MR, its therapy remains problematic. Annuloplasty has limitations because it does not completely address the fundamental problem of ischemic ventricular distortion. The present approach directly reverses this distortion in an adjustable manner to reposition the PMs and achieve normal mitral leaflet closure. Although surgical infarct plication can similarly reduce ischemic MR,<sup>21</sup> the proposed device is relatively simple and provides direct and reversible control over PM repositioning. It does not compromise LV systolic function or raise filling pressures, because the patch is applied to the most abnormal, infarcted portion of the ventricle, and the LV is shifted to a lower-volume operating point.

This approach has the potential to minimize the factors that most deter surgeons from repairing ischemic MR at the time of coronary revascularization (uncertain result and need for

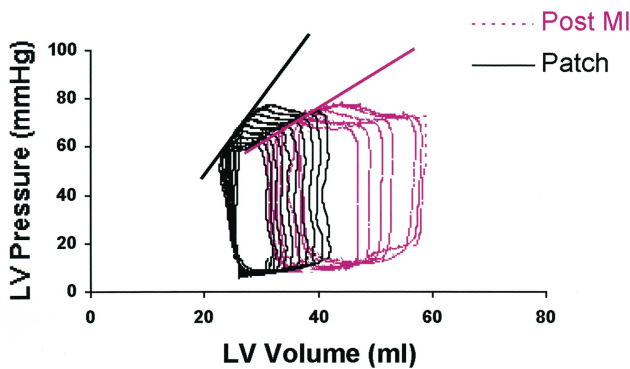
cardiac incision with cardiopulmonary bypass). It is an additional example of the increasing role of echocardiography in guiding successful application of new, less invasive methods in the beating heart.<sup>1,2</sup> This approach allows real-time monitoring by echo, permitting adjustment tailored to the individual heart. In addition, imaging can allow the surgeon to assess the degree of adjustment necessary to achieve efficacy by manual compression of the myocardium overlying the PMs. Epicardial imaging was used because of the difficulty imaging the midline sheep heart from the esophagus, but in patients, transesophageal guidance could be used.

### Limitations and Additional Directions

The clinical spectrum of ischemic MR includes varying location and chronicity of ischemia and PM geometry. The purpose of this study, however, was specifically to explore the ability of an external device to reduce MR in a model with increased leaflet tethering attributable to ischemic ventricular distortion. Our study achieved this in both acute and chronic models of inferobasal ischemia resembling the pattern seen in many patients with ischemic MR. Future work can address the potential for this approach in global LV dysfunction, in which the major determinant of MR remains displacement of the PMs, which are located in the posterior portion of the



**Figure 6.** Changes in 3D mitral valve geometry with displacement of the ischemic medial PM (green) reversed by patch placement (right).



**Figure 7.** Pressure-volume loops in one sheep showing end-systolic pressure-volume relationship and end-diastolic pressure-volume relationship after MI.

LV<sup>8</sup>; one large or two smaller balloons may be indicated to reposition both PMs symmetrically. Although the present device does not directly involve the annulus, it could, if necessary, be extended toward the base to reduce annular size as well when the annulus is prominently dilated, as in chronic global dysfunction. Although decreased LV contractile function can also contribute to ischemic MR,<sup>26,27</sup> this becomes important primarily when tethering is increased, making it harder for the LV to close the valve; the most straightforward remedy is to normalize tethering mechanically.<sup>8,21</sup>

There has been extensive clinical experience with epicardial patches for defibrillation<sup>28</sup> and pseudoaneurysm repair<sup>29</sup> without decreased LV function or increased arrhythmias. Initial reports of passive containment devices for treating heart failure, such as the Acorn device extending around both ventricles to the atrioventricular groove, suggest they are well tolerated by patients without clinical evidence of constriction.<sup>30,31</sup> Patch placement may in fact provide additional benefits by limiting ventricular remodeling. Localized patching of anterior infarcts that do not generate MR has been shown to limit the global dilatation and dysfunction that occur in remodeling; decreasing MR would compound this benefit.<sup>32,33</sup> The apparent occasional increases in contractility are similar to those described by Burkhoff and Ratcliffe, with reduction in LV size and wall stress by partial ventriculectomy.<sup>34,35</sup>

## Summary

An external device that repositions the PMs can reduce ischemic MR without compromising LV function. This relatively simple technique demonstrates the ability of echocardiographic imaging to promote the use of such less invasive techniques by guiding their application in the beating heart.

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