Persistent Reduction of Ischemic Mitral Regurgitation by Papillary Muscle Repositioning

Judy Hung, MD; Miguel Chaput, MD; J. Luis Guerrero, BS; Mark D. Handschumacher, BS; Lampros Papakostas, MD; Suzanne Sullivan, BS; Jorge Solis, MD; Robert A. Levine, MD

Background—Recurrent ischemic mitral regurgitation (IMR) is frequent despite initial reduction by annuloplasty because continued LV remodeling increases tethering to the infarcted papillary muscle (PM). We have previously shown that PM repositioning by an external patch device can acutely reduce IMR. In this study, we tested the hypothesis that IMR reduction persists despite possible continued LV remodeling.

Methods and Results—In 7 sheep, we used a chronic ischemic posterior infarct model that produces LV dilatation and MR over 10 weeks. An epicardial patch device was adjusted under echo guidance to reduce MR, with follow-up over a further 8 weeks and evaluation by 3D echo and sonomicrometry. In all 7 sheep, moderate IMR resolved with acute patch application and PM repositioning (6.5±1.8 mm to 0.6±1.3 mm proximal jet width, P<0.001) without decrease in LVEF (43±3% to 44±8%). Eight weeks after PM repositioning, MR was not significantly greater (0.6±1.3 mm versus 1.0±1.0 mm, P=NS) despite an increase in LV volumes in 3 animals (2 had increases of 50±15%). On average, LV volumes did not change significantly (ESV: 46±8 mL versus 49±15 mL; P=NS and EDV: 85±16 mL versus 89±30 mL; P=NS). LVEF was unchanged from acute to chronic patch (44±8% versus 43±8%). Contractility as end-systolic elastance did not decrease from the chronic MI to the acute and chronic patch stages, nor were there any significant changes in dP/dt, LV stiffness constant, or time constant of LV relaxation (Tau). Conclusion—PM repositioning is persistently effective in reducing moderate chronic IMR, even when LV volume increases. This may reflect structural stabilization by an external patch device of the papillary muscle-LV wall complex that controls mitral valve tethering. (Circulation. 2007;116[suppl I]:I-259–I-263.)

Key Words: mitral regurgitation • left ventricular remodeling

Ischemic mitral regurgitation (MR) is a common complication of coronary artery disease that doubles late mortality.1–4 Extensive evidence has shown that ischemic MR results from LV distortion, which displaces the papillary muscles (PMs) and tethers the mitral leaflets apically, restricting their closure.5–12 A key element in the pathogenesis of ischemic MR, therefore, is distortion of the papillary muscle-mitral valve complex that controls and restricts leaflet closure, as proposed by Komeda, Miller, and colleagues.10

Therapy for ischemic MR remains problematic. Mitral ring annuloplasty, often applied at the time of bypass surgery, reduces annular size but does not directly address the broader problem of ischemic left ventricular distortion with tethering; its benefits are therefore incomplete,13–15 particularly when LV remodeling continues to progress postoperatively.16,17 Uncertain benefit and the need for atrial incision and cardiopulmonary bypass can deter surgical repair. We have previously shown that a patch-balloon device placed externally over the myocardium to reposition the underlying papillary muscles can acutely reduce ischemic mitral regurgitation.18 Adjusting a Dacron patch containing an inflatable balloon locally reverses LV remodeling and repositions the infarcted papillary muscle toward the anterior mitral annulus, thereby reducing leaflet tethering and MR (Figure 1) acutely. This approach directly targets tethering, and has allowed individual titration under echocardiographic guidance in the beating heart to restore papillary muscle-mitral valve geometry acutely.

The chronic efficacy of this device, however, is unclear, especially given the possibility of continued LV remodeling. In this study, we therefore examined the chronic efficacy of a patch-balloon device placed externally over the papillary muscles, hypothesizing that structural stabilization of the papillary muscle-ventricular complex results in persistent reduction of ischemic mitral regurgitation.

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I-259
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), including the infarcted and border zone regions, 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). The Dacron patch buttresses the balloon so that its inflation displaces the myocardium inward toward the anterior mitral annulus. Patch placement and degree of balloon inflation were guided in situ by echocardiography to reduce MR and achieve normal leaflet seating by injecting the minimum amount of saline necessary (0 to 15 mL, in 2 to 5 mL increments). This procedure permitted immediate adjustment of the device if necessary before repeat imaging and hemodynamics.

Data Collection and Analysis

LV pressure was recorded along with an ECG lead on a multichannel physiological recorder (Sonometrics Inc). 2D, Doppler, and 3D echo data were collected using a high-frequency (3.5 to 5 MHz) TEE multiplane probe (Philips Medical Systems) 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 Philips 5500 sector scanner with 3D software to record rotated images at angular increments of 4°. 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 off-line using customized software. MR was quantitated by measuring the vena contracta (narrowest jet origin) in a long-axis view perpendicular to the coaptation line, averaged in 3 cardiac cycles. Vena contracta width ≥5 mm was considered moderate in degree. LV and Mitral Valve 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. Device application was adjusted to reduce MR based on visual assessment of the proximal jet width.

Mitral valve tethering geometry was measured in 5 of 7 animals in which there were technically adequate images. Papillary muscle tethering distance was measured in the apical long axis view from the tip of the infarcted papillary muscle to anterior medial trigone. The angle between the posterior and anterior mitral leaflet and line of the mitral annulus were measured in the apical long axis and tenting area was measured in the apical 4 Chamber view as described by Magne et al.

Methods

As detailed by Llaneras et al., anesthesia was induced in 7 Dorsett hybrid sheep with sodium thiopental (12.5 mg/kg IV), and the trachea intubated and ventilated at 15 mL/kg with a mixture of 2% isoflurane and oxygen. All animals received glycopyrrolate (0.4 mg IV) and vancomycin (0.5 gm IV) 1 hour before incision. The heart was exposed by a sterile left thoracotomy. A micromanometer-tipped Millar catheter was placed in the LV to measure pressure, dP/dt, and tau. Sonomicrometry crystals were placed as described below for pressure-volume loop studies.

Chronic MR was produced by ligating the second and third circumflex obtuse marginal branches via left thoracotomy. After hemodynamic measurements and echocardiographic imaging, the incision was closed and the animals cared for over 10 weeks to allow mitral regurgitation to develop. A second thoracotomy was then performed for placement of the patch-device to reduce MR, guided by concomitant imaging. Animals were then cared for over 8 weeks, after which imaging and hemodynamic measurements were repeated after a third thoracotomy. Data acquisition with echocardiographic imaging and hemodynamics, including sonomicrometry, was therefore performed at 4 stages: baseline, chronic MR, acute patch, and chronic patch (Figure 2). This study was reviewed and approved by our institutional Animal Care Committee.

Figure 1. Epicardial echocardiography 8 weeks after inferior infarction (left) and acutely after balloon-patch device placement (right). Before patching, the inferior wall bulges out, the posterior PM is displaced away from the annulus, and severe MR is seen. After patching, the inferior wall is straightened, the PM is realigned, and MR is absent. LV indicates left ventricle; Ao, aorta.

Figure 2. Study design. Seven sheep had inferior infarct creation by circumflex ligation. Ten weeks later, an epicardial inflatable patch-balloon device was applied to the infarct and inflated under echo guidance to eliminate MR. Animals were reassessed 8 weeks after for chronic efficacy of the device. Echocardiography was performed at baseline. Echocardiography and sonomicrometry data were collected after chronic MR (pre-patch), acutely after patching and chronically after patching. LA indicates left atrium; Ao, aorta; PM, papillary muscle.
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 (ESPVR, or elastance, Emax) 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 LVP to LV volume, and the end-systolic points fitted to a linear equation; its slope was taken as a measure of contractile state.25 End-diastole was defined by the trough in the LVP tracing after atrial contraction. The end-diastolic pressure-volume relationship (EDPVR) data from curve-fitting parameters, x is the LV volume, and C is the stiffness constant.23 The relaxation time constant (tau) was calculated as the time for LVP to fall from peak negative dP/dt to half its value.26 Preload-recruitable stroke work (PRSW) as a measure of LV contractility that incorporates variation in load was defined as the slope relating LV stroke work (SW) and end-diastolic volume (EDV): SW = PRSW x (EDV + Vn), where Vn is the x-intercept.27

Statistical Analysis
The efficacy of the patch-balloon device was tested by repeated measures analysis of variance (baseline, post-MR, acute patch, and chronic patch). Significant differences were examined by paired t-test, using Fisher F test criterion for multiple comparisons. A 2-tailed probability value of 0.05 was considered significant.

Statement of Responsibility
The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results
All 7 sheep developed moderate or greater mitral regurgitation 10 ± 3 weeks after infarction (proximal jet width 6.5 ± 1.8 mm). Before patch placement, left ventricular volumes had increased in all animals compared with baseline (ESV 46.2 ± 14.6 mL versus 28.1 ± 8.9 mL, P = 0.045, EDV 85.5 ± 23.8 mL versus 54.7 ± 13.2 mL, P = 0.035). Acutely after patch placement, all sheep had a significant reduction in MR with proximal jet of MR decreasing to 0.6 ± 1.3 mm (trace MR, P < 0.001). After 8 ± 2 weeks of chronic patch placement, MR did not increase in any animal (proximal jet = 1.0 ± 1.0 mm, P = NS).

As expected, there was a significant decrease in LV EF from baseline to the chronic infarct and MR stage (49 ± 3% versus 43 ± 3%, P = 0.03, Figure 3). After acute and chronic patch placement, there was no significant change in LVEF (43 ± 3% versus 44 ± 8%, P = NS). Mean LV volumes were also unchanged acutely after patch placement and after 8 weeks follow-up. In 4 of the 7 sheep, EDV and ESV decreased or remained unchanged after chronic patch placement, whereas they increased in 3 (2 had increases of 50 ± 15%), consistent with continued remodeling (Figure 4). Despite this, none of the animals had recurrent MR. Figure 5 shows the persistent reduction in MR in an animal where patching has resulted in persistent reverse remodeling of the infarcted papillary muscle, although the overall LV volume has increased.
LVSP, mm Hg 83
14 108
17 111
HR, beats per minute 107
27 NS
108
/L11006

LV hemodynamics
Heart rate and systolic and diastolic blood pressure were unchanged at all stages after chronic MR development (Table 1). Maximal dP/dt did not change significantly after patching or at chronic follow-up. The elastance (Emax) and preload-recruitable stroke work rose slightly but not significantly after chronic patching. There were also no significant changes in tau or diastolic stiffness constant at chronic follow-up compared with acute patch or chronic MR stage before patch.

Mitral Valve Geometry
After acute patch, there were decreases in papillary muscle tethering distance, anterior and posterior leaflet angles, and leaflet tenting area (Table 2) consistent with favorable changes in mitral valve and papillary muscle geometry after patch placement. This effect was maintained with chronic patch placement.

Discussion
The results of this study show that external infarct patching using an adjustable device to reposition the papillary muscle is effective in treating ischemic MR chronically over 10 weeks of follow-up without detrimental effects on LV function and without recurrent MR.

Mechanistic Implications
These findings further demonstrate the importance of LV remodeling and distortion of the mitral apparatus in the pathogenesis of ischemic MR. Our data support the hypothesis that structural stabilization of the valvular-ventricular complex by applying a repositioning and restraining device over the infarcted wall can restore mitral leaflet coaptation and prevent MR. This suggests that persistent reverse remodeling can be achieved with this device.

Overall, LV volumes did not increase after external patch placement. Interestingly, in 3 of 7 animals, volumes continued to increase despite patch placement at long-term follow-up. Despite this increase, MR did not recur. This suggests that structural stabilization of the valvular-ventricular complex or restoration of the geometric relationship between the infarcted wall and mitral annulus successfully eliminates ischemic MR, even in the face of increased global LV size. Assessment of symmetric versus asymmetric tethering is an important concept, but one that could not be directly compared in our study as the experimental model used was an asymmetric model in terms of segmental infarct and papillary muscle involvement; whether this approach will work in a more symmetric model needs to be further explored.

Occasional volume increases can be explained by variable remodeling among individual animals and by the local application of the patch in this series. As previously shown, similar infarcts in different subjects can lead to different myocardial injuries and hence variable remodeling results. In this series, we used a patch locally applied to the infarct site and border zone, potentially explaining continued global dilatation in some animals. The continued LV remodeling that occurred in 3 animals was most likely attributable to myocardial factors, whereas continued LV remodeling in patients on conventional therapy is often attributable to the recurrence of mitral regurgitation with further LV dilation.

Variation may reflect the degree of border zone coverage and stress reduction, as well as biological variability in intrinsic myocardial susceptibility to remodeling and heart failure—for example, based on adrenergic responsiveness or response to mechanical stress.

Patch alone without balloon over the PM to assess remodeling restraint was not specifically addressed in our model. However, other studies in which a mesh is sewn over an infarction have demonstrated reduced MR or remodeling. Ideally the patch-balloon device can be applied without the need for concurrent annuloplasty, although one could also use external patch in combination with MV annuloplasty.

Other groups have suggested that remodeling still occurs in patients with ischemic MR despite successfully treating regurgitation. In our series, overall, LV volumes did not increase and, most importantly, indices of LV function were stabilized chronically by the device. Overall, none of the sheep exhibited the fully developed picture of remodeling with decreased systolic function, EF, elastance, or PRSW chronically after placement. These results are therefore consistent with those of Kelley et al and Moainie et al that

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<th>TABLE 1. Hemodynamic Measurements</th>
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<td>HR, beats per minute</td>
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<td>LVSP, mm Hg</td>
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<td>LVEDP, mm Hg</td>
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<td>Max dP/dt, mm Hg/s</td>
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<td>PRSW, W/mL</td>
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<td>Tau, ms</td>
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P values for the overall repeated-measures ANOVA are shown. HR indicates heart rate; LVSP, LV systolic blood pressure; LVEDP, LV end-diastolic blood pressure; Emax, systolic elastance; PRSW, preload recruitable stroke work.

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<th>TABLE 2. Changes in Mitral Valve Geometry With Patch Balloon Device</th>
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<td>Stage</td>
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<td>Tethering Length, mm</td>
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<td>Tenting Area, cm²</td>
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<td>Anterior angle, degree</td>
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<td>Posterior angle, degree</td>
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#P<0.05 Chronic MR vs Acute Patch; *P<0.05 Chronic MR vs Chronic Patch; P=NS for acute patch vs chronic patch for all measurements. MR indicates mitral regurgitation.
Hung et al Persistent Reduction of MR With Patch-Device I-263

external infarct constraint limits not only MR but also global LV remodeling and contractile dysfunction. Also, no chronic increase in LV stiffness or relaxation time was observed, suggesting that local application of the device does not impair global LV diastolic function and filling.

Clinical Implications

Despite the clinical importance of ischemic mitral regurgitation, its therapy remains uncertain. Mitral ring annuloplasty does not directly address the fundamental problem of ischemic ventricular distortion. This approach provides therapy which directly reverses this distortion and with chronic efficacy. Furthermore, this approach has potential minimally invasive applications, minimizing surgical risks factors that can deter surgeons from repairing ischemic MR in a more ill patient population who ironically may most benefit from a reduction in MR.

Conclusion

In summary, papillary muscle repositioning has persistent efficacy in reducing chronic MR (despite occasionally increased LV volumes). This effect may be related to structural stabilization of the valvular-ventricular complex.

Sources of Funding

This work was supported in part by NIH/National Institute for Biomedical Imaging and Bioengineering (NIBIB) R21 EB005294 (to J.H.) and NIH/ National Heart Lung Blood Institute (NHLBI) RO1 038176 (to R.A.L.), and an American Society of Echocardiography Career Development Award (to M.C.).

Disclosures

None.

References

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