Percutaneous Mitral Valve Repair for Chronic Ischemic Mitral Regurgitation
A Real-Time Three-Dimensional Echocardiographic Study in an Ovine Model

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Background—Although surgical annuloplasty is the standard repair for ischemic mitral regurgitation (IMR), its application is limited by high morbidity and mortality. Using 2D and real-time 3D echocardiography in an ovine model of chronic IMR, we evaluated the geometric impact and short-term efficacy of a percutaneous transvenous catheter-based approach for mitral valve (MV) repair using a novel annuloplasty device placed in the coronary sinus.

Methods and Results—Six sheep developed IMR 8 weeks after induced posterior myocardial infarction. An annuloplasty device optimized to reduce anterior-posterior (A-P) mitral annular dimension and MR was placed percutaneously in the coronary sinus. Mitral annular A-P and commissure-commissure dimensions and MV tenting area (MVTa) in 3 parallel A-P planes (medial, central, and lateral) were assessed by real-time 3D echocardiography with 3D software. The annuloplasty device reduced MR jet area from 5.4±2.6 to 1.3±0.9 cm² (P<0.01), mitral annular A-P dimension in both systole and diastole (24.3±2.5 to 19.7±2.4 mm; P<0.03; 31.0±3.9 to 24.7±2.1 mm; P<0.001), and MVTa at mid systole in all 3 planes (153±46 to 93±24 mm², P<0.01; 140±47 to 88±23 mm², P<0.03; and 103±23 to 87±26 mm², P<0.03).

Conclusions—Percutaneous coronary sinus–based mitral annuloplasty reduces chronic IMR by reducing mitral annular A-P diameter and MVTa. This suggests the potential clinical application of a new nonsurgical therapeutic approach in patients with IMR. (Circulation. 2005;111:2183-2189.)

Key Words: catheters ▪ echocardiography ▪ mitral valve ▪ myocardial infarction ▪ regurgitation

Ischemic mitral regurgitation (IMR), a consequence of left ventricular (LV) dysfunction despite a structurally normal mitral valve (MV), occurs in 19% of patients after myocardial infarction (MI).1,2 Chronic IMR is an independent predictor of mortality; the greater the degree of mitral regurgitation (MR) is, the worse the prognosis is.3 Although surgical annuloplasty is the current standard treatment for IMR, the high morbidity and mortality associated with the surgical procedure limit its application in patients with IMR.4–6 These findings point to the need for the development of alternative approaches for treatment of IMR.

See p 2154

Human IMR is a complex phenomenon that is related to alterations in annular and ventricular geometry.7–13 Using real-time 3D (RT3D) echocardiography, we demonstrated that medial MV tenting area (MVTa) is an important determinant of MR severity in IMR.13 Clinical experience and experimental study,14 however, have demonstrated that reducing the distance between the anterior and posterior annulus (A-P diameter) by surgical annuloplasty reduces or eliminates IMR. These findings are related because it is likely that increasing leaflet coaptation by reducing mitral annular A-P dimension simultaneously reduces tenting area. Continued study of IMR in both human and experimental models with RT3D echocardiography is necessary to characterize and quantify these relationships.

Recently, several groups have reported development of percutaneous catheter-based approaches to mitral annuloplasty (PTMA) that exploit the anatomic proximity of the coronary sinus (CS) to the mitral apparatus.15,16 These studies in animal models of acute IMR and rapid pacing-induced heart failure demonstrated the feasibility of CS-based annuloplasty. However, it is essential to explore this approach in relevant models of chronic IMR similar to the human clinical situation.4–6 The ovine with posterior MI is considered to be
an established IMR model. The purpose of the present study was to evaluate the feasibility and short-term efficacy of a percutaneous transvenous catheter-based annuloplasty for MV repair in an ovine model of chronic IMR using 2D and RT3D echocardiography.

Methods

Animal Preparation for MI

IMR was created in sheep using the model of Llaneras et al. All animals were studied in compliance with the Principles of Laboratory Animal Care formulated by the National Society of Medical Research and the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health. A total of 31 Dorsett sheep (57 to 68 kg) were intubated, and anesthesia was induced with ketamine 100 mg/mL (11 mg/kg) and xylazine 20 mg/mL (0.11 mg/kg) with continuous hemodynamic and ECG monitoring. Anesthesia was maintained with isoflurane (1.5% to 3%). Through a left lateral thoracotomy, snares were placed around the proximal second and third obtuse marginal branches of the circumflex coronary artery to maintain hemodynamic stability. Posterior MI was created by coronary artery occlusion with tightening of these snares. After coronary artery occlusion, animals were monitored for 2 hours, and the thoracotomy was then closed. In surviving animals, MR was assessed by echocardiography at 4 and 8 weeks after MI.

Of 31 sheep subjected to this protocol, 12 died either immediately or within 1 month of MI, and 11 failed to develop MR that was 2+ or greater within 8 weeks. Thus, 8 animals survived and developed IMR that was 2+ or greater. Because of poor echo windows, 2 of these animals were excluded from further study. The remaining 6 served as subjects for the evaluation of the feasibility and short-term efficacy of percutaneous annuloplasty in chronic IMR. At a minimum of 8 weeks after MI, animals were returned to the cardiac catheterization laboratory for assessment of IMR and device implantation.

Echocardiographic Assessment

On the day of device implantation, animals were placed in the right lateral decubitus position and studied by conventional 2D and RT3D echocardiography at baseline and immediately after device implantation with a Sonos 7500 ultrasound system (Philips). A phased-array 3.5- to 5-MHz probe and a matrix-array handheld transducer (x4 transducer) were used to obtain 2D and RT3D echo images, respectively. All 3D echo images were stored digitally on a compact disk; all 2D echo images were stored digitally on magneto-optical disks for offline analysis. The degree of MR was graded by an MR jet area using color Doppler technique with 2D echocardiography in the parasternal long-axis view, with the integrated evaluation program in the ultrasound system.

We used 3D computer software (TomTec, Co) to evaluate LV wall motion and dimensions, left atrial dimensions, and geometry of the mitral apparatus. To evaluate the geometry of the mitral apparatus, first, 2D diameters of the mitral annulus (A-P and commissure-commissure [C-C]) at systole and diastole were assessed (Figure 1). Next, 3 A-P equidistant parallel planes perpendicular to the C-C plane were defined for imaging the geometry of the medial, central, and lateral sides of the mitral leaflets as described in our previous study (Figure 1). At mid systole, MVTa, the area enclosed by the annular plane and 2 leaflets, and MV tenting height (MVTht) were measured in all 3 A-P planes (Figure 1). The same echocardiographic protocol was completed in 6 control sheep without MI to compare measurements between normal sheep and those with IMR.

Device Implantation

IMR animals were intubated and anesthetized as described previously on the day of device implantation. After baseline echocardiography, a 9F introducer sheath was placed in the left internal jugular vein and advanced into the CS. Coronary venography was performed through this sheath. The anterior interventricular branch of the great cardiac vein was identified and engaged with a standard exchange-length Glidewire (Boston Scientific). Over this wire, a multilumen 9F custom delivery catheter (Viacor, Inc) was advanced into the CS until the distal tip was in the anterior interventricular vein. Annuloplasty devices were introduced into the CS through the lumens of the custom catheter under fluoroscopic guidance (Figure 2).

Each annuloplasty device is fabricated from a single piece of drawn nitinol wire to a particular length and stiffness profile. In our method, we can vary the number of devices (up to 3) and stiffness of each device in the multilumen custom catheter (Figure 2). With these combinations, the total stiffness can be magnified 6-fold, increasing the force delivered to the posterior mitral annulus. When positioned in the CS, the annuloplasty devices effected a graded conformational change in the mitral annulus that reduced A-P diameter and increased leaflet coaptation. Devices were added or interchanged systematically in the 9F multilumen custom delivery catheter to optimize the reduction in A-P mitral annular dimension and MR degree under the monitoring by 2D echocardiography. After each annuloplasty device adjustment, 2D and RT3D echocardiographic images were obtained. When maximum reduction of MR was achieved, the devices were left in place for 30 minutes. During each experiment, the degree of MR was enhanced by administering neosynephrine and intravenous lactated Ringer’s solution. Safety of diagnostic, temporary implantation of the PTMA device was assessed by pathological examination after the PTMA procedure. After temporary device placement, animals were euthanized at 7 days (n=3), 14 days (n=2), or 28 days

Figure 1. Schematics of C-C plane and 3 A-P planes (left) and geometric measurements of mitral annulus (left) and MV (right). Moving and rotating cut planes on cross-sectional 3D image at MV level give C-C plane connecting both commissures and 3 A-P planes in medial (M), central (C), and lateral (L) sides of MV. AML indicates anterior mitral leaflet; PML, posterior mitral leaflet; Ao, aorta; LA, left atrium; and MVTht, MV tenting height.
(n=1). Excised hearts were examined by a trained pathologist blinded to treatment.

Safety of Long-Term Device Implantation
To assess the safety of long-term implantation, in 5 animals without MR, a prototype implant (9F in 3, 7F in 2) was placed. The animals were euthanized for histopathological examination at 50 days after implantation.

Statistical Analysis
All values are expressed as mean ± SD. An unpaired t test was used to compare normal animals with those with IMR; a paired t test was used to compare MR with mitral annular diameter before and after device implantation in animals with IMR. RT3D echocardiographic variables in all 3 A-P planes during device implantation in animals with IMR were evaluated by repeated-measures ANOVA, testing for the mitral annuloplasty effect, local effect in 3 A-P planes, and their interaction. Fisher’s protected least-significant-difference test was used for the post hoc test. A value of P < 0.05 was considered statistically significant.

Results

Changes in LV Chamber and Mitral Annulus in IMR
Coronary artery occlusion produced posterior LV wall motion abnormalities. Compared with normal sheep, those with IMR had increased LV and left atrial diameters and decreased posterior LV wall thickness (Table 1). Compared with normal sheep, those with IMR had increased A-P mitral annular diameter at both diastole and systole (31.0±3.9 versus 24.2±2.5 mm and 24.3±2.5 versus 18.8±2.1 mm; P < 0.01 for both) and increased C-C mitral annular diameter in systole (28.5±3.1 versus 23.7±2.0 mm; P < 0.01).

Mitral Valvular Deformation in IMR
In normal sheep, there was no difference in MV Th and MVTa between the echocardiographic planes (Table 2). In contrast, in sheep with IMR, there were asymmetric changes in MV tenting, with increased MVT Th and MVTa in the medial plane compared with the lateral plane. Compared with normal sheep, those with IMR had larger MVT Th and MVTa in medial and central planes and larger MVTa in all planes.

Impact of Annuloplasty
Placement of the annuloplasty device reduced MR jet area from 5.4±2.6 to 1.3±0.9 cm² (P < 0.01) (Figure 3 and Table 3). The mitral annular A-P diameter was significantly reduced both in systole (24.3±2.5 to 19.7±2.4 mm; P < 0.03) and diastole (31.0±3.9 to 24.7±2.1 mm; P < 0.001) by device implantation, although the mitral annular C-C diameter was increased.

| Table 1. LV, Left Atrial, and Mitral Annular Diameter in Normal Sheep and Those With IMR |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                | Normal (n=6)    | IMR (n=6)       | P               |
| LV, mm                         |                 |                 |                 |
| IVSt                           | 8.5±1.0         | 9.0±1.1         | NS              |
| PWT                            | 8.2±1.2         | 5.8±1.2         | <0.01           |
| LVDd                           | 47.2±3.9        | 59.0±5.2        | <0.01           |
| LVDs                           | 32.2±4.3        | 47.0±6.6        | <0.001          |
| WMSI                           | 1±0.0           | 1.30±0.14       | <0.001          |
| LAD, mm                        | 28±3            | 42±10           | <0.03           |
| MA diameter, mm                |                 |                 |                 |
| A-P diastolic                  | 24.2±2.5        | 31.0±3.9        | <0.01           |
| A-P systolic                   | 18.8±2.1        | 24.3±2.5        | <0.01           |
| C-C diastolic                  | 30.5±2.2        | 33.5±2.9        | NS              |
| C-C systolic                   | 23.7±2.0        | 28.5±3.1        | <0.01           |

IVSt indicates interventricular septal thickness; PWT, posterior wall thickness; LVDs, LV systolic diameter; LVDd, LV diastolic diameter; WMSI, wall motion score index; LAD, left atrial diameter; and MA, mitral annular.
unaffected (Table 3). In terms of mitral valvular geometry, MVTht and MVTa in all 3 A-P planes were significantly decreased by device implantation (Figures 4 and 5). Annuloplasty device placement caused greater reductions in MVTht and MVTa in the medial A-P plane than in the lateral A-P plane (\(P < 0.05\) and \(P < 0.01\); Figures 4 and 5). Annuloplasty device implantation did not cause significant changes in heart rate (101 to 99 bpm), systemic blood pressure (systolic, 149/46 to 137/36 mm Hg; diastolic, 93/38 to 92/41 mm Hg), or ST segments on ECG. In each case, the CS was patent without perforation after temporary device placement. There was no damage to the MV, the LV, or adjacent coronary arteries.

**Safety of Long-Term Device Implantation**

In each case, the PTMA device was encapsulated and covered by an endothelial lining. The CS was patent without perforation, and there was no damage to the MV, the LV, or adjacent coronary arteries. There was no migration of the device during this time period.

**Discussion**

The key finding of this animal study is that PTMA acutely reduced IMR by shortening the mitral annular A-P diameter and reducing MVTa, particularly at the medial aspect. Furthermore, 50 days after device implantation, the animals revealed no major complications on histopathological examination.

**Table 2. Differences in Mitral Valve Tenting Between Normal Sheep and Those With IMR**

<table>
<thead>
<tr>
<th></th>
<th>Normal (n=6)</th>
<th>IMR (n=6)</th>
<th>(P)</th>
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<tbody>
<tr>
<td>MVTht, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial</td>
<td>6.3±1.0</td>
<td>9.5±1.6*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Central</td>
<td>6.3±1.0</td>
<td>8.8±1.7</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Lateral</td>
<td>6.5±1.5</td>
<td>7.5±1.4</td>
<td>NS</td>
</tr>
<tr>
<td>MVTa, mm²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial</td>
<td>77±5</td>
<td>153±46*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Central</td>
<td>82±8</td>
<td>140±47</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Lateral</td>
<td>80±6</td>
<td>103±23</td>
<td>&lt;0.05</td>
</tr>
</tbody>
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\(*P < 0.05\) vs lateral value in IMR sheep.

**Table 3. Effect of Annuloplasty on Mitral Annular Diameter and MR**

<table>
<thead>
<tr>
<th></th>
<th>Baseline, mm</th>
<th>Treatment, mm</th>
<th>(P)</th>
</tr>
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<tbody>
<tr>
<td>Mitral annular diameter, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A-P diastolic</td>
<td>31.0±3.9</td>
<td>24.7±2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A-P systolic</td>
<td>24.3±2.5</td>
<td>19.7±2.4</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>C-C diastolic</td>
<td>33.5±2.9</td>
<td>32.2±3.9</td>
<td>NS</td>
</tr>
<tr>
<td>C-C systolic</td>
<td>28.5±3.1</td>
<td>26.0±2.8</td>
<td>NS</td>
</tr>
<tr>
<td>MR jet area, cm²</td>
<td>5.4±2.6</td>
<td>1.3±0.9</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

IMR is a major and growing clinical problem. Recent reports document that 7 800 000 Americans suffer MI annually\(^{20}\); 19% of these can be expected to develop significant MR.\(^{1,2}\) Although MV dysfunction increases symptoms of heart failure and reduces survival in these patients, the MR is rarely addressed directly. Surgical annuloplasty is currently the only option for treatment, but this operation is associated with high morbidity and mortality, limiting its application.\(^{4–6}\) However, patients who survive surgery frequently derive clinical benefit from the surgical annuloplasty.

Several potential mechanisms, including subvalvular papillary muscle displacement, which causes leaflet tenting, contribute to malcoaptation of the mitral leaflets in chronic IMR.\(^{7–13}\) Despite this mechanistic complexity, annuloplasty alone produces satisfactory reduction of IMR in up to 80% of cases.\(^{21}\) This suggests that development of less invasive and safer methods of mitral annuloplasty might afford an important clinical benefit for large numbers of patients with IMR. There is currently great interest in using the CS to facilitate such approaches.

The CS is located in the atria-ventricular groove parallel to the posterior mitral annulus. The venous confluence runs from the CS ostium in the right atrium to the origin of the anterior interventricular vein, following the course of the posterior mitral annulus nearly from commissure to commissure. This anatomic proximity of the CS to the mitral annulus led to the hypothesis that mitral annuloplasty could be performed percutaneously by placement of a device in the CS. Percutaneous placement of mitral annuloplasty devices in the CS has been reported to reduce MR in models of global LV dysfunction\(^{15}\) and acute

**Figure 3.** Annuloplasty device significantly reduced MR jet area and A-P diameter in mitral annulus (right) vs baseline (left) in chronic IMR. LA indicates left atrium.
ischemia. Results from experimental models are encouraging. However, mechanisms that underlie these experimental forms of MR may differ from those present in chronic IMR. As for the difference between MR associated with global LV dysfunction and IMR, both MV anatomy and mitral annular geometry were different between them, suggesting potentially different approaches of PTMA in these 2 types of MR. As for the difference between acute and chronic IMR, it was demonstrated that fibrous annular perimeter was dilated and height of the mitral annulus was reduced in ovine models with chronic IMR, whereas they were unchanged in acute IMR. Moreover, it is known that LV dilatation and corresponding mitral annular geometric change after MI play an important role in the production of chronic IMR. Investigating the efficacy of PTMA in chronic IMR is clinically relevant because we often encounter patients with chronic IMR and consider the use of PTMA. This study was performed in an ovine model of chronic IMR. With occlusion of the obtuse marginal branches of the circumflex coronary artery, this ovine model is thought to be similar to human IMR caused by posterior MI. In this study, sheep with IMR had systolic and diastolic LV diameters (47±7 and 59±5 mm) similar to those observed in human IMR (50±1 and 64±1 mm). That human clinical study with RT3D echo demonstrated increased mitral annular diameter and asymmetrical MV deformation (more severe tenting at the medial side than the lateral side) in IMR; in contrast, leaflet tenting was symmetrical in dilated cardiomyopathy. The present study in sheep with chronic IMR revealed similarities to human chronic IMR, including similar mitral annular dilatation and asymmetric MV deformation (more severe tenting at the medial than the lateral side). Thus, the animal model of chronic IMR used in this study closely approximates that observed in humans.

Various geometric deformations, including degree of MV tenting, have been linked to severity of human IMR. Excess

![Figure 4](image-url) - RT3D echocardiographic images of MV during mid systole in medial (left), central (middle), and lateral (right) A-P planes at baseline (top) and after device implantation (bottom). MV tenting (top arrow) was significantly improved in medial A-P plane by device implantation in CS (lower arrow) vs lateral A-P plane. LA indicates left atrium.

![Figure 5](image-url) - Impact of device implantation on MV tenting. Device implantation reduced all measures of tenting. However, ANOVA revealed greater reduction in MVTh and MVTa in medial A-P plane vs lateral A-P plane. *P<0.01 vs baseline; †P<0.03 vs baseline; ‡P<0.05 vs baseline.

Figure 4. RT3D echocardiographic images of MV during mid systole in medial (left), central (middle), and lateral (right) A-P planes at baseline (top) and after device implantation (bottom). MV tenting (top arrow) was significantly improved in medial A-P plane by device implantation in CS (lower arrow) vs lateral A-P plane. LA indicates left atrium.

Figure 5. Impact of device implantation on MV tenting. Device implantation reduced all measures of tenting. However, ANOVA revealed greater reduction in MVTh and MVTa in medial A-P plane vs lateral A-P plane. *P<0.01 vs baseline; †P<0.03 vs baseline; ‡P<0.05 vs baseline.
tenting of the MV is strongly associated with the degree of functional MR in patients with systolic LV dysfunction. In one study of IMR, MVTa in the medial A-P plane was the strongest determinant of MR severity. This MV tenting is present in the ovine model of chronic IMR. In this model, reducing the distance between the A-P annulus by surgical annuloplasty reduces or eliminates MR. In the present study of IMR, 2D and RT3D echo demonstrated reduction in both MV tenting, particularly at the medial side, and A-P mitral annular diameter by a CS-based, percutaneous annuloplasty. The annuloplasty device effectively improved the asymmetric deformation of MV. These changes in the geometry of the mitral apparatus are believed to contribute to the reduction in IMR, similar to the effect observed with open surgical annuloplasty.

Study Limitations
This is an acute preliminary study of the feasibility and efficacy of percutaneous transvenous annuloplasty in an ovine model of chronic IMR. Long-term safety and efficacy of the device were not evaluated in animals with chronic IMR, although no major complications or migration was found in those without MR. Detailed studies of hemodynamic impact of percutaneous annuloplasty were not investigated. Chronic implantation studies are now underway to address these concerns.

In humans, the CS runs in close proximity to the circumflex coronary artery in the AV groove. This may introduce potential risk of damage to the circumflex coronary artery by placement of an annuloplasty device in the CS. Therefore, coronary angiography and venography before deployment of such a device in CS, as in this study, are necessary to avoid damage to the coronary circulation. As noted, long-term studies are warranted to confirm safety of CS-based mitral annuloplasty.

In this study, we did not evaluate anatomic differences in CS and mitral anatomy in sheep and humans. However, the CS has close proximity to the mitral annulus in humans, suggesting the feasibility of human percutaneous annuloplasty.

Finally, we estimated MR severity by MR jet area by color Doppler technique. This method could be problematic in some cases. Because MR was not very severe in this study, it was difficult to obtain clear flow convergence even when the aliasing velocity was lowered. It was also difficult to obtain regurgitant volume by quantitative pulsed-Doppler methods by transthoracic echocardiography. As a result, we had to abandon more quantitative measurements of MR severity. However, detecting significant reductions in the color jet area to observe the efficacy of the device was relatively easy. This simple method was quite useful for this purpose.

Conclusions
The present study showed that percutaneous mitral annuloplasty using a novel device reduces MR by reducing MV tenting and mitral annular A-P diameter in an ovine model of chronic IMR. Further development and clinical trials of percutaneous annuloplasty are warranted.

Disclosure
Drs Liddicoat, Cohn, and Gillinov have equity interests in Viacor, Inc. Drs Shiota and Hayase have served as consultants to Viacor, Inc.

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