Impact of Papillary Muscle Relocation as Adjunct Procedure to Mitral Ring Annuloplasty in Functional Ischemic Mitral Regurgitation

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Background—The optimal surgical treatment in functional ischemic mitral regurgitation (FIMR) remains controversial. Recently, a posterior papillary muscle relocation (PMR) technique as adjunct procedure to ring annuloplasty has been proposed to prevent recurrent FIMR. In the present study, we used 3D cardiac MRI to assess the impact of relocating both papillary muscles as adjunct procedure to downsized ring annuloplasty on mitral leaflet coaptation geometry in FIMR pigs.

Methods and Results—Eleven FIMR pigs were randomized to downsized ring annuloplasty (RA; n=6) or RA combined with PMR (RA+PMR, n=5). In the RA+PMR group, a 2-0 Gore-Tex suture was attached to each trigone, exteriorized through the corresponding papillary muscle, mounted on an epicardial pad, and tightened to relocate the myocardium adjacent to the anterior and posterior papillary muscles 5 and 15 mm, respectively. Using 3D MRI, the impact from these interventions on leaflet geometry was assessed. The distance from the posterior papillary muscle to the anterior trigone was reduced significantly more (median values) in the RA+PMR compared with RA animals at end-diastole (−7.9% versus 3.8%, P<0.01) and end-systole (−9.7% versus 2.5%, P=0.02). Accordingly, lateral tethering of the coaptation point (median values) was reduced significantly more in RA+PMR compared with RA animals (−42.8% versus −29.1%, P<0.01).

Conclusions—Adding papillary muscle relocation to downsized ring annuloplasty reduced lateral leaflet tethering in a porcine experimental model of FIMR. Therefore, this technique holds promise for reducing persistent and recurrent FIMR in patients. (Circulation. 2009;120[suppl 1]:S92–S98.)

Key Words: animals ischemia mitral valve papillary muscles regurgitation surgery

Recent years have seen the adoption of a more aggressive surgical approach in patients with chronic functional ischemic mitral regurgitation (FIMR), but controversy prevails as to what constitutes optimal treatment.1 Current standard treatment is to implant a rigid planar annuloplasty ring that uses downsizing of the mitral annulus to increase leaflet coaptation area. This treatment most often abolishes perioperative FIMR; however, mitral regurgitation persists or reappears late after ring annuloplasty in 13% to 59% of cases.2 Clinical3 and experimental in vivo4 and in vitro5 studies demonstrate in concert that 2 central pathways may cause FIMR, namely annular dilatation and papillary muscle (PM) displacement. Annular dilatation is sufficiently corrected by ring annuloplasty, but PM displacement is not. Accordingly, the high incidence of recurrent FIMR after ring annuloplasty has been attributed to restricted leaflet mobility,6 augmented posterior leaflet tethering,7 continued left ventricular (LV) remodeling,8 and reduced coaptation forces,5 among others. A number of recent experimental and clinical studies have assessed the beneficial effects of addressing LV remodeling and PM displacement to relieve FIMR. Elevation of the inferior LV wall, on which the PMs are attached, toward the mitral annulus has been performed in experimental9 and clinical10,11 studies using different surgical techniques. Most notably, a direct PM relocation technique was introduced by Kron et al,12 who used a felt pledgeted suture to pull the posterior PM (PPM) tip toward the mitral annulus near the posterior commissure as adjunct procedure to ring annuloplasty in chronic FIMR patients. The technique was further evaluated in 2 other clinical studies showing reversal of FIMR in all patients at 2 to 16 months of follow-up.13,14 However, a few drawbacks in these studies should be noted: The PPM tips were pulled toward the annulus, which transfers force to a single geometric point to relieve mitral leaflet...
tethering, thereby inducing high PM myocardial tissue stresses. Second, only PPM relocation was performed, although anterior PM (APM) displacement intuitively also carries the potential to induce additional leaflet tethering. Third, the impact on mitral valve leaflet and subvalvular geometry from PM relocation was not assessed.

To overcome these limitations, we used cardiac MRI to assess the impact on the entire mitral valve apparatus from adding both APM and PPM relocation to ring annuloplasty. PM relocation was obtained by tightening sutures from the annular trigones to epicardial pads applying compressive forces on the LV wall adjacent to the PMs.

**Methods**

This study was conducted as a chronic intervention/control study on Danish landrace pigs. All animal experiments were conducted according to the guidelines given by the Danish Inspectorate for Animal Experimentation and after specific approval from this institution. Qualified animal caretaker personnel monitored the health status of the animals at all times during the study period. Analgesics were administered whenever animals showed any sign of pain. In case of refractory pain or poor thriving animals were euthanized.

**Chronic FIMR Experimental Model**

The chronic FIMR animal model has recently been developed at our institution.15,16 Figure 1 displays exclusion and inclusion of animals. Ninety pigs of 50 kg were preanesthetized with intramuscular injections of midazolam (0.5 mg/kg) and ketamine (5 mg/kg). Intravenous access was obtained through an ear vein, and Hypnorm (0.6 mg/kg) were given to allow intubation. The animal was sedated and intubated, and coupled to a ventilator. In 24 pigs, transthoracic echocardiography revealed FIMR (moderate or more severe). The animals were then examined by cardiac MRI, awakened, and returned to the farming facilities. Two animals died during the following week of heart failure.

**Figure 1. Flow sheet.**

![Flow sheet](image)

One week after the cardiac MRI examination, 22 FIMR animals were returned to the laboratory. Before surgery, 10 animals were randomized for ring annuloplasty alone (RA) and 12 for RA in combination with PM relocation (RA + PMR), using block randomization (Figure 2). The pigs were sedated, intubated, and coupled to a ventilator. Cefuroxime (1.5 g intravenously) was administered before and after surgery. Postoperative medication consisted of paracetamol (4×1 g) and amiodarone (200 mg) daily for 5 days. Flunixin (0.4 mg/kg intramuscular) was given if necessary. Furosemide (2×40 mg) and potassium chloride (2×750 mg) were given during the period of intermittent pacing. Twenty-eight animals were lost because of heart failure. Thirty-one animals survived 6 weeks to be returned to the laboratory and were sedated, intubated, and coupled to a ventilator. In 24 pigs, transthoracic echocardiography revealed FIMR (moderate or more severe). The animals were then examined by cardiac MRI, awakened, and returned to the farming facilities. Two animals died during the following week of heart failure.

**Mitrail Valve Surgery**

One week after the cardiac MRI examination, 22 FIMR animals were returned to the laboratory. Before surgery, 10 animals were randomized for ring annuloplasty alone (RA) and 12 for RA in combination with PM relocation (RA + PMR), using block randomization (Figure 2). The pigs were sedated, intubated, and coupled to a ventilator. Cefuroxime (1.5 g intravenously) was administered before and after surgery. Propofol (5 mg/kg/h), fentanyl (15 µg/kg/h), and pancuronium (0.2 mg/kg intravenously) were given to allow sternotomy. Heparin (40 000 units) was given, cannulas were placed in the ascending aorta and right atrium, and cardiopulmonary bypass was established. The aorta was clamped and cardioplegia (1000 mL +300 mL/20 minutes) was administered into the aortic root. A left atriotomy was done, and in the RA + PMR group a 2–0 Gore-Tex suture was passed through each trigone. The anterior trigone (Atrig) stitch was passed through the APM tip and posterior trigone (Ptrig) stitch through the PPM tip to the epicardial side. In both groups, an annuloplasty ring was implanted in the mitral annulus. Using a standard Edward sizing kit, the ring sizing was based on an integrated assessment of intertrigonal distance and anterior leaflet height. Downsizing of the annuloplasty ring by 2 sizes was performed to compensate for leaflet tethering. In the RA group, 6 animals received a size 26 ring and 3 received a size 28 ring. In the RA + PMR group, 8 animals received a size 26 ring and 3 received a size 28 ring. One animal in each group died before cardiopulmonary bypass was established.

Because cardiac MRI was used, metal core rings were not applicable and therefore plastic casts of the Carpenter Edwards
Classic annuloplasty ring were used. The Gore-Tex stitches were tied to the ring, the atriotomy was closed and after 1 hour of reperfusion, animals were weaned from cardiopulmonary bypass, and the venous cannula was removed. Each Gore-Tex suture was attached to an epicardial pad, allowing gradual tightening to relocate the PMs toward the anterior annulus. The APM and PPM epicardium was relocated 5 and 15 mm closer to the Atrig and Prig, respectively. Two custom-made sliding calipers were constructed (Figure 3) and attached to the papillary muscle relocation stitches at each papillary muscle. Through a string of pearls and a pad overlying the epicardium, it was possible to obtain very precise relocation of the myocardium overlying the papillary muscles by moving the sliding caliper. To detect when a force was applied and thereby identify baseline of relocation, a strain gauge was attached on the sliding caliper in series with the string of pearls.

The aortic cannula was removed, protamine sulfate (40 000 units antitheparin) was administered, hemostasis was secured, drains were placed, and the sternum was closed. After 2 to 4 hours of hemodynamic stabilization, animals were awakened, extubated, and returned to the farming facilities.

One RA animal died as a result of a ruptured LV from sternotomy and 1 RA+PMR animal died as a result of a ruptured aorta during cannulation. Six animals (1 RA, 5 RA+PMR) died a few hours after surgery of heart failure refractory to inotropic support. One RA animal died the first postoperative day of heart failure, and 1 RA+PMR animal died 1 week after surgery during the cardiac MRI examination as the result of ventricular fibrillation before data were acquired. Autopsies were performed on all dead animals. Pericardial tamponade was observed in 1 RA+PMR animal. No animals had papillary muscle rupture.

Twelve animals completed cardiac MRI examination 1 week after surgery, but 1 animal was excluded because of ring fracture. The following medications were administered for the rest of the study period: pfoodocillin (200 mg), amiodarone (200 mg), fentanyl patch (100 µg/h), fluixin (0.4 mg/kg intramuscular), paracetamol (2×2 g), buprenorphine (30 µg/kg intramuscular) if necessary, furosemide (2×40 mg), and potassium chloride (2×750 mg).

**Data Acquisition and Analysis**

**Echocardiography**

At baseline and 6 weeks after the infarction, transthoracic echocardiography of the mitral valve was performed to identify animals with a regurgitant jet. One week later, sternotomy and epicardial echocardiography was performed to allow grading of mitral valve regurgitation according to American Heart Association/American College of Cardiology guidelines. Twenty-one weeks after surgery, trace

**Cardiac MRI**

MRI was conducted with a Philips Achieva 1.5-T MR Scanner (Philips, Best, Netherlands). ECG was used to synchronize data acquisition. Cine images were used to assess hemodynamics and mitral valve leaflet motion. All cine images were acquired with the balanced steady-state free-precession sequence using 30 heart phases; a slice thickness of 5 mm; pixel size, 2.0×2.0 mm²; repetition time, 3.2 ms; echo time, 1.6 ms; and flip angle, 65°. Aortic flow (A-flow) was assessed using a 2D phase contrast sequence with a slice thickness of 8 mm; pixel size, 2.5×2.5 mm²; repetition time, 5.1 ms; echo time, 3.1 ms; flip angle, 15°; and velocity encoding of 100 cm/s, which was sufficient to prevent aliasing in all scans. Three-dimensional morphology scans were acquired with the Balanced Steady-State-Free-Precession sequence. The field-of-view was 330×330×300 mm³; repetition time, 4.0 ms; echo time, 2.0 ms; and flip angle, 90°. Online identification of end-diastole and end-systole was necessary for planning of 3D morphology scans. End-diastole was defined as the time of R-wave onset in the ECG and end-systole defined as the time of maximum septal contraction.

**Hemodynamics**

LV stroke volume (LVSv) was obtained by subtracting LV volume at end-diastole (LVEDV) and end-systole (LVESV), based on a 12-slice cine short-axis scan covering the LV from the apex to the center of the atrium. Mitral valve regurgitation volume (RegVol) and fraction (RegFract) were obtained by subtracting the LVSV from the A-flow. None of the animals had aortic regurgitation. The LV sphericity index was calculated as the ratio between the LV volume and a sphere with a diameter corresponding to the base-apex distance on a long-axis cine scan at end-diastole (SphED) and end-systole (SphES).

**Papillary Muscle Position**

Three-dimensional morphology cardiac MRI was performed with isotropic resolution of 1.72 mm along the 3 main axes, allowing extraction of any imaging plane within the imaging volume (Cardiac3D, Systematic Software Engineering, Aarhus, Denmark). The software used to analyze the 3D morphology scans allowed identification of any plane in the imaging volume. This allowed identification of the mitral annular plane, which was then translated into the left ventricle. The papillary muscle tips were defined as the first substantial part seen of each papillary muscle.
The spatial position of the APM and PPM, Atrig, Ptrig, and the posterior mitral annulus was defined at end-diastole and end-systole, and corresponding coordinates (x, y, z) were transferred to mathematical analysis software (LabVIEW 8.0; National Instruments, Austin, Tex). All distances between PMs and trigone points were calculated.

Mitral Leaflet Coaptation Geometry
Mitral valve geometry analysis was based on 12 cine scans rotated to cover the mitral valve at end-systole (Figure 4). Using dedicated software (SISview, MR-Research Centre, Aarhus University Hospital, Skejby, Denmark) leaflet contours were manually marked and reconstructed 3-dimensionally to assess occlusional leaflet area (OLA), that is, surface area of the leaflet contour for a given leaflet coaptation geometry and tenting volume (TentVol). Coaptation points corresponding to the anterolateral (A1-P1), middle (A2-P2), and posteromedial (A3-P3) leaflet segments were identified to measure the mean tenting height (THmean) between the leaflet coaptation point and annular plane and mean coaptation length (CLmean) between leaflet tip and coaptation point. Coaptation geometry analysis for each segment was calculated as the average of data from three images rotated 15° to cover 45° of the mitral annulus. In the septolateral plane, the distance from the anterior annulus to the coaptation point (CoaptDispl) was measured as an indicator of lateral leaflet tethering (Figure 5).

Statistics
Data analysis was done using STATA software version 9.2. The significance level was 5%. The low number of animals in each group made it difficult to assume normal distribution of data and therefore nonparametric testing at least 4 animals in each group is necessary to show statistically significant differences. We planned for 6 animals in each group to compensate for the risk of outliers. However, because of a high mortality rate, only 5 animals were included in the RA+PMR group. We considered a difference in “changes induced by surgery” of 10% as clinically meaningful.

Hemodynamics, PM position, and mitral leaflet geometry were assessed before and after surgery to compare relative changes ((postoperative−preoperative)/preoperative×100) in the RA+PMR and RA groups. Survival in the RA and PMR groups was compared using the Fisher exact test.

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

Results
Survival
Although not statistically significant, the 1-week postoperative survival in the RA+PMR (5/12) was lower than in the RA group (7/10) (P=0.23).

Hemodynamics
Hemodynamic variables and surgically induced changes derived from cardiac MRI are listed in Table 1. There were no statistically significant differences between groups.

Papillary Muscle Position
Table 2 reveals statistically significantly higher PPM relocation toward the Atrig in the RA+PMR compared with RA group at end-diastole and end-systole.

Mitral Leaflet Coaptation Geometry
Table 3 shows end-systolic mitral leaflet geometry before and after surgery. Lateral tethering of the coaptation point (CoaptDispl) was significantly reduced in the RA+PMR animals compared with RA animals. Furthermore, a general tendency of improved overall leaflet coaptation geometry was observed in the RA+PMR animals in terms of more negative OLA and TentVol ranges compared with RA animals. However, there was no statistically significant difference in segmental leaflet geometry between groups.

Discussion
PM relocation was achieved by transmyocardial 2–0 Gore-Tex sutures anchored epicardially corresponding to each PM and fixated on the annuloplasty ring at the respective trigone taking the following factors into consideration: Previous geometric analysis of the porcine FIMR model compared nonparametric testing at least 4 animals in each group is necessary to show statistically significant differences. We planned for 6 animals in each group to compensate for the risk of outliers. However, because of a high mortality rate, only 5 animals were included in the RA+PMR group. We considered a difference in “changes induced by surgery” of 10% as clinically meaningful.

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Discussion
PM relocation was achieved by transmyocardial 2–0 Gore-Tex sutures anchored epicardially corresponding to each PM and fixated on the annuloplasty ring at the respective trigone taking the following factors into consideration: Previous geometric analysis of the porcine FIMR model compared
with healthy controls revealed that 12-mm relocation of the PPM in direction of PPtrig would be necessary to alleviate the posterolateral PPM displacement observed, whereas 8.6-mm relocation of the APM in direction of the Atrig was necessary to alleviate the apical APM displacement. However, in this posterior LV wall infarct model, we considered PPM displacement as the primary geometric culprit lesion, whereas the APM displacement may reflect a general LV remodeling effect as the result of persistent MR and may be alleviated by relieving MR. On the basis of these considerations, we decided to relocate the APM 5 mm and PPM 15 mm toward the respective trigone.

The impact on PM position and mitral leaflet geometry was assessed using 2D cine and 3D morphology cardiac MRI. In the RA+PMR group, a clear tendency was observed toward relocation of both PMs closer to the anterior mitral annulus, which caused a significant reduction in lateral leaflet tethering (CoaptDispl). Furthermore, and a general tendency of improved overall leaflet coaptation geometry was observed in the RA+PMR animals in terms of more negative OLA and TentVol ranges compared with RA animals. Theoretically, this may reflect a more uniform coaptation geometry in the RA+PMR animals.

We observed a postoperative mortality rate of 58% in the RA+PMR group compared with 30% in the RA group. Although not statistically significant, the difference could explained by longer cardiopulmonary bypass and cross-clamp time, disturbed myocardial contractility, or myocardial ischemia caused by compression of coronary artery branches by the epicardial pads. Furthermore, compression on the epica-

### Table 1. Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>Change Induced by Surgery, %</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>RA</td>
<td>RA+PMR</td>
</tr>
<tr>
<td>Weight</td>
<td>55.2 [53.0; 57.0]</td>
<td>53.8 [50.0; 57.0]</td>
</tr>
<tr>
<td>EDV</td>
<td>171.2 [139.9; 203.5]</td>
<td>169.6 [141.6; 208.4]</td>
</tr>
<tr>
<td>ESV</td>
<td>107.5 [81.7; 134.1]</td>
<td>109.3 [87.9; 142.9]</td>
</tr>
<tr>
<td>SV</td>
<td>63.8 [57.3; 2.1]</td>
<td>60.3 [53.7; 65.5]</td>
</tr>
<tr>
<td>EF</td>
<td>37.6 [32.5; 1.7]</td>
<td>35.8 [31.4; 38.1]</td>
</tr>
<tr>
<td>HR</td>
<td>62.7 [53.0; 2.0]</td>
<td>66.4 [51.0; 80.0]</td>
</tr>
<tr>
<td>CO</td>
<td>4.0 [3.1; 4.7]</td>
<td>4.0 [2.7; 5.2]</td>
</tr>
<tr>
<td>A-flow</td>
<td>53.2 [41.8; 61.9]</td>
<td>46.9 [43.7; 48.4]</td>
</tr>
<tr>
<td>Reg vol</td>
<td>10.5 [5.9; 17.7]</td>
<td>13.5 [6.6; 18.0]</td>
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<tr>
<td>Reg fract</td>
<td>16.7 [10.3; 29.7]</td>
<td>21.9 [12.2; 27.8]</td>
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<tr>
<td>SpHED</td>
<td>60.3 [45.9; 81.1]</td>
<td>77.2 [47.9; 108.9]</td>
</tr>
<tr>
<td>SpHES</td>
<td>52.3 [43.6; 63.2]</td>
<td>62.6 [31.9; 99.4]</td>
</tr>
</tbody>
</table>

Medians and ranges of values are displayed. HR indicates heart rate; CO, cardiac output; A-flow, aortic flow.

*Relative change (%) induced by surgery in RA+PMR versus RA group.

### Table 2. Papillary Muscle Distances to Anatomic Landmarks

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>Changes Induced by Surgery, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RA</td>
<td>RA+PMR</td>
</tr>
<tr>
<td>End-diastole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APM-PPM</td>
<td>38.8 [35.0; 46.6]</td>
<td>42.7 [38.6; 46.5]</td>
</tr>
<tr>
<td>APM-Atrig</td>
<td>31.6 [23.1; 36.0]</td>
<td>29.4 [25.9; 39.0]</td>
</tr>
<tr>
<td>APM-PPtrig</td>
<td>42.7 [37.8; 46.2]</td>
<td>41.7 [40.0; 48.3]</td>
</tr>
<tr>
<td>PPM-Atrig</td>
<td>45.1 [39.5; 54.8]</td>
<td>48.7 [44.2; 56.9]</td>
</tr>
<tr>
<td>PPM-PPtrig</td>
<td>40.7 [32.1; 42.9]</td>
<td>39.5 [34.9; 50.7]</td>
</tr>
<tr>
<td>Atrig-PPtrig</td>
<td>22.4 [19.8; 24.5]</td>
<td>22.8 [22.3; 23.6]</td>
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<tr>
<td>End-systole</td>
<td></td>
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<td>APM-PPM</td>
<td>35.9 [31.8; 44.8]</td>
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</tr>
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<td>22.2 [20.2; 24.6]</td>
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</table>

Medians and ranges of values are displayed. APM indicates anterior papillary muscle.

*Relative change (%) induced by surgery in RA+PMR versus RA group.
dium increases the radii of curvature locally on the left ventricular wall. According to the law of Laplace, this will increase wall tension, which may lead to myocardial ischemia and ischemia-induced ventricular arrhythmia, exacerbate LV remodeling, and increase risk of myocardial wall rupture.

Surgical PM relocation toward the annulus using sutures was first introduced in 2002 by Kron et al. In 18 chronic FIMR patients a felt pledgetted suture from the PPM tip to the epicardial side. This approach allowed transesophageal pads on the myocardium overlying the papillary muscles to be addressed. Theoretically, a traction suture from the PPM tip to the mitral annulus will facilitate leaflet coaptation. However, the epicardial compression implies a theoretical risk of increased LV wall stress, myocardial ischemia and arrhythmia, LV rupture, and deterioration of LV function. These potential serious complications need to be further addressed before clinical implementation. However, the pres-
ent study has demonstrated that papillary muscle relocation is targeting the subvalvular component of FIMR and therefore holds promise in preventing persistent and recurrent FIMR after ring annuloplasty.

**Study Limitations**

The pathogenesis of chronic FIMR in the present study is different from the clinical setting with older patients, gradually increasing coronary artery stenosis and development of myocardial arterial collateral blood supply. Therefore, the surgically induced changes in mitral leaflet coaptation geometry observed in this study might not be reproducible in chronic FIMR patients.

The very high mortality rate from ischemia and tachycardial stress may limit the external validity of the model. Furthermore, the tendency toward a higher mortality in the RA + PMR group meant that more animals were allocated to this group. Accordingly, a selection bias could be present so that surviving animals in this group were in better constitution (stronger strain, smaller infarct size, and so forth) than in the RA group. However, Table 1 does not indicate that a difference was present in baseline hemodynamic values between groups.

The time from surgery to postoperative cardiac MRI examination was 1 week, and this short time span probably did not allow for any long-term differences between RA and RA + PMR groups to develop. In the clinical setting, a much longer follow-up time of months to years probably would be necessary to show a potential difference in freedom from recurrent chronic FIMR. In this study, postoperative data in groups of 5 and 6 animals were obtained. These low numbers induce a risk of type II statistical error.

**Conclusion**

Adding papillary muscle relocation to downsized ring annuloplasty reduced lateral leaflet tethering and showed a tendency toward improved leaflet coaptation geometry in a porcine experimental model of FIMR. Therefore, this technique holds promise for reducing persistent and recurrent FIMR in patients.

**Sources of Funding**

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**Disclosures**

Drs Smerup, Nielsen, and Hasenkam are co-owners of ENOVACOR ApS. Drs Jensen and Wierup received a consulting fee from Heart Beat Medical Technology.

**References**


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