PRECLINICAL RESEARCH

Acute and Chronic Reduction of Functional Mitral Regurgitation in Experimental Heart Failure by Percutaneous Mitral Annuloplasty

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OBJECTIVES We sought to determine acute and chronic efficacy of a percutaneous mitral annuloplasty (PMA) device in experimental heart failure (HF). Further, we evaluated the potential for adverse effects on left ventricular (LV) function and coronary perfusion.

BACKGROUND Reduction of mitral annular dimension with a PMA device in the coronary sinus may reduce functional mitral regurgitation (MR) in advanced HF.

METHODS Study 1: a PMA device was placed acutely in anesthetized open-chest dogs with rapid pacing-induced HF (n = 6) instrumented for pressure volume analysis. Study 2: in 12 anesthetized dogs with HF, fluoroscopic-guided PMA was performed, and dogs were followed for four weeks with continuing rapid pacing.

RESULTS Study 1: percutaneous mitral annuloplasty reduced annular dimension and severity of MR at baseline and with phenylephrine infusion to increase afterload (MR jet/left atrial [LA] area 26 ± 1% to 7 ± 2%, p < 0.05). Pressure volume analysis demonstrated no acute impairment of LV function. Study 2: no device was placed in two dogs because of prototype size limitations. Attempted PMA impaired coronary flow in three dogs. Percutaneous mitral annuloplasty (n = 7) acutely reduced MR (MR jet/LA area 43 ± 4% to 8 ± 5%, p < 0.0001), regurgitant volume (14.7 ± 2.1 ml to 3.1 ± 0.5 ml, p < 0.05), effective regurgitant orifice area (0.13 ± 0.010 cm² to 0.040 ± 0.003 cm², p < 0.05), and angiographic MR grade (2.8 ± 0.3 device to 1.0 ± 0.3 device, p < 0.001). In the conscious state, MR was reduced at four weeks after PMA (MR jet/LA area 33 ± 3% HF baseline vs. 11 ± 4% four weeks after device, p < 0.05)

CONCLUSIONS Percutaneous mitral annuloplasty results in acute and chronic reduction of functional MR in experimental HF. (J Am Coll Cardiol 2004;44:1652–61) © 2004 by the American College of Cardiology Foundation

Patients with dilated cardiomyopathy due to ischemia or primary myocardial disease develop secondary “functional” mitral regurgitation (MR). The putative mechanisms are enlargement of the mitral annulus caused by ventricular and atrial dilation, dysfunction of the papillary muscles second-

ary to conformational changes of the enlarged left ventricle (LV), and disturbances in the normal contraction sequence of the different myocardial segments (1). Chronic volume overload associated with MR in the failing heart can exacerbate the hemodynamic strain on the failing LV, contributing to further LV remodeling, worsening symptoms, and reduced survival.

Surgical repair of the mitral valve via placement of an annuloplasty ring has been demonstrated to improve symptoms, and possibly survival, in patients with severe LV dysfunction and advanced heart failure (HF) (2). However, widespread use of surgical mitral annuloplasty as a “stand-alone” therapy for advanced HF has been limited because of concern regarding the significant morbidity and mortality associated with surgical procedures in this patient population.

The coronary sinus (CS) follows a circumferential course on the atrial side of the atrioventricular groove at a distance of 10 to 14 mm along the posterolateral aspect of the mitral annulus (3). The relationship of the CS to the mitral annulus has led investigators to develop CS devices that can reduce mitral annular dimension and offer the potential for percutaneous mitral annuloplasty (PMA). If effective, PMA may offer the hemodynamic benefit of reduction of MR without the inherent risks of cardiac surgery in patients with advanced HF. In the 15% of patients with a left dominant coronary circulation, the circumflex coronary artery (CX) parallels the entire length of the posterior leaflet. In patients

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with a right dominant coronary circulation, the intimate relationship of the CX to the CS is most pronounced in the distal CS, near the anterior commissure of the mitral valve. The CX crosses superior to the CS in ~33% of cases and between the CS and the annulus in the remaining 67% of cases (4,5). Thus, compression of the circumflex with the tension applied via the CS is a potential concern. The objectives of this study were to determine if placement of a novel annuloplasty device (Fig. 1) in the CS would result in acute and chronic reduction in the severity of functional MR associated with chronic experimental HF in dogs. Further, we sought to determine if adverse effects on LV function or coronary flow were associated with device placement.

**METHODS**

Two studies were performed. In the first study, dogs with experimental HF produced by rapid ventricular pacing were anesthetized, underwent sternotomy, and were instrumented for pressure volume (sonomicrometry crystals) analysis and epicardial echocardiography. The acute effects of PMA on annular dimension, MR severity, and hemodynamics were assessed at baseline and during after-load increases produced by phenylephrine. In the second study, dogs with experimental HF underwent conscious echocardiography to assess MR severity and LV function and then underwent PMA under fluoroscopic guidance with assessment of coronary flow, mitral regurgitation severity (con-}

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**Abbreviations and Acronyms**

- **CS**: coronary sinus
- **CX**: left circumflex coronary artery
- **ERO**: effective regurgitant orifice
- **HF**: heart failure
- **LA**: left atrium/atrial
- **LV**: left ventricle/ventricular
- **MR**: mitral regurgitation
- **PISA**: proximal isovelocity surface area
- **PMA**: percutaneous mitral annuloplasty

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**Experimental HF with Functional MR.** We utilized a modification of the rapid pacing model of cardiomyopathy (6). Dogs were anesthetized with ketamine (10 mg/kg), diazepam (0.5 mg/kg), and isoflurane (0.5% to 2.5%). Via a left thoracotomy, a pacing lead was placed on the right ventricle. After two weeks, the pacemaker was programmed at progressively higher rates: 180 beats/min for two weeks, 200 beats/min for one week, 210 beats/min for one week, 220 beats/min for one week, and 240 beats/min for one week.

**Acute Experimental Protocol.** The pacemaker was turned off and animals were anesthetized with fentanyl (0.25 mg/kg) and midazolam (0.75 mg/kg) followed by infusion of fentanyl (0.18 mg/kg/h) and midazolam (0.59 mg/kg/h), intubated, and ventilated. Via a sternotomy, ultrasonic crystals (Sonometrics Corporation, London, Canada) were placed on the endocardial surface and intramyocardially in the long and short axis of the LV through stab wounds. Micromanometer-tipped catheters (Millar Instruments, Houston, Texas) were placed in the LV via the right femoral artery and in the left atrium (LA) via the LA appendage and calibrated. Hemodynamic data and epicardial echocardiographic images were obtained immediately before and after placement of the annuloplasty device under basal conditions and during intravenous infusion of phenylephrine to increase afterload.

**Placement of the Annuloplasty Device.** A guide catheter was positioned in the CS through the right external jugular vein. The device was advanced up to the turning point of the great cardiac vein (referred to as the distal CS henceforth) into the anterior interventricular groove. The distal anchor of the device was deployed and traction was applied on the proximal end, simulating the conformational change induced by deployment of the proximal anchor (i.e., the device was cinched). After data collection, the traction was released and a phenylephrine continuous infusion (10–µg/min and increasing by 10–µg/min increments to achieve increases in systolic LV pressure of 30 mm Hg) was started. Intravenous atropine was administered if bradycardia occurred. Once the target pressure was achieved, collection of hemodynamic and echocardiographic data was repeated before and after applying traction on the proximal end of the device (device cinching).

**Hemodynamic Analysis.** Pressure and dimension signals were acquired and analyzed with CardioSoft (Sonometrics...
Table 1. Effect of Annuloplasty Device on Hemodynamics and MR in the Absence and Presence of Phenylephrine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Device</th>
<th>Phenylephrine</th>
<th>Phenylephrine + Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak LV pressure (mm Hg)</td>
<td>87.3 ± 4.9</td>
<td>88.3 ± 6.2</td>
<td>117.7 ± 10.6†</td>
<td>118.6 ± 11.2</td>
</tr>
<tr>
<td>LV minimum pressure (mm Hg)</td>
<td>4 ± 0.8</td>
<td>3.2 ± 1.2</td>
<td>7.6 ± 2.0</td>
<td>8.2 ± 3.5</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>11.3 ± 2.5</td>
<td>10.1 ± 2.7</td>
<td>19.3 ± 2.7‡</td>
<td>19.2 ± 3.3</td>
</tr>
<tr>
<td>Mean LA pressure (mm Hg)</td>
<td>8.7 ± 1.4</td>
<td>8.2 ± 1.1</td>
<td>12.1 ± 1.0</td>
<td>11.6 ± 1.8</td>
</tr>
<tr>
<td>+ dP/dt (mm Hg/s)</td>
<td>933 ± 94</td>
<td>845 ± 153</td>
<td>1,385 ± 194‡</td>
<td>1,368 ± 187</td>
</tr>
<tr>
<td>Tau (ms)</td>
<td>64 ± 15</td>
<td>57 ± 8</td>
<td>98 ± 28</td>
<td>100 ± 27</td>
</tr>
<tr>
<td>LV end-diastolic volume (ml)</td>
<td>91.8 ± 10.1</td>
<td>88.8 ± 11.9</td>
<td>100.9 ± 9.6‡</td>
<td>100.5 ± 9.8</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>24 ± 5</td>
<td>26 ± 6</td>
<td>27 ± 5</td>
<td>25 ± 4§</td>
</tr>
<tr>
<td>LV stroke volume (ml)</td>
<td>20.8 ± 4.1</td>
<td>23.2 ± 6</td>
<td>27.3 ± 6.4</td>
<td>24.3 ± 0.2§</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>26 ± 5</td>
<td>27 ± 5</td>
<td>27 ± 5</td>
<td>25 ± 4§</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>1.8 ± 0.3</td>
<td>2.3 ± 0.4</td>
<td>2.2 ± 0.4</td>
<td>2.0 ± 0.4§</td>
</tr>
<tr>
<td>Mitral annulus diameter (cm) ¶</td>
<td>2.7 ± 0.2</td>
<td>2.3 ± 0.1*</td>
<td>2.7 ± 0.1</td>
<td>2.3 ± 0.1§</td>
</tr>
<tr>
<td>MR jet area (cm²)</td>
<td>2.2 ± 0.7</td>
<td>0.5 ± 0.2*</td>
<td>3.3 ± 0.5</td>
<td>0.8 ± 0.2§</td>
</tr>
<tr>
<td>MR jet/LA area (%)</td>
<td>16 ± 4</td>
<td>4 ± 1†</td>
<td>26 ± 1‡</td>
<td>7 ± 2§</td>
</tr>
</tbody>
</table>

*p < 0.05 versus baseline; †p < 0.05 versus baseline; ‡p < 0.05 versus baseline; ¶p < 0.05 versus phenylephrine. ¶The mitral annulus diameter in normal dogs (n = 8) is 2 ± 0.1 cm.

LA = left atrial; LV = left ventricular; MR = mitral regurgitation.

Corporation, London, Ontario, Canada) as previously reported to yield LV volumes and parameters of systolic and diastolic function (7).

ECHOCARDIOGRAPHIC ANALYSIS. Epicardial two-dimensional and color flow images were obtained and analyzed off-line with a commercially available console and analysis system (Vingmed System Five and EchoPAC, GE Medical Systems, Milwaukee, Wisconsin). Para-apical images were analyzed. The largest diastolic diameter of the mitral annulus, the largest MR jet area, and the corresponding LA area were measured. The severity of MR was assessed by the MR jet area/LA area ratio (8).

Study 2. Experiments were performed in 12 mongrel dogs (20 to 30 kg). The study was performed in three phases that included slightly different prototypes of the device (Phase 1 [prototype 1, n = 4], Phase 2 [n = 2, prototype 2], and Phase 3 [n = 6, prototype 3]).

STUDY PROTOCOL. Heart failure was induced by the modified pacing protocol described earlier and all dogs had an additional week of pacing at 200 beats/min before device placement. Echocardiography was performed on each dog before initiation of pacing and at the end of pacing protocol.

Animals were taken to the catheterization laboratory where implantation of the device was performed under anesthesia and its efficacy measured with the pacemaker off (sinus rhythm). After device placement, the animals were allowed to recover for three days and then pacing was resumed at 200 beats/min. Transthoracic echocardiography was performed after four weeks and animals were sacrificed.

PLACEMENT OF DEVICE. Anesthesia was induced by ketamine (10 mg/kg) or diazepam (0.5 mg/kg) and was maintained with isoflurane (0.5% to 2.5%). The left femoral artery and right jugular vein were surgically isolated and cannulated with a 9F sheath. Left ventricular pressure was measured at baseline and after device placement. Contrast ventriculography was performed at baseline and after device placement. Transthoracic echocardiography was performed and mitral annular dimension and MR severity (MR jet area/LA area) were assessed as described earlier. Proximal isovelocity surface area (PISA) measurements were made at baseline and after device therapy. The jet area was also assessed intermittently during device placement to assess efficacy with variations in placement of the device. Under fluoroscopic guidance, the CS was cannulated with a flexible guidewire.

Table 2. Cardiac Structure and Function of MR at Baseline, After Induction of Heart Failure, and 4 Weeks After Device Implantation Procedure in Dogs That Did (n = 7) or Did Not (n = 3) Receive a Mitral Annuloplasty Device

<table>
<thead>
<tr>
<th>Echocardiographic Parameter</th>
<th>LVEDD (cm)</th>
<th>Left Atrial Area (cm²)</th>
<th>Ejection Fraction (%)</th>
<th>MR Jet Area/LA Area</th>
<th>Mitral Annulus (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device implanted (n = 7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.29 ± 0.08</td>
<td>16.3 ± 0.7</td>
<td>68 ± 2</td>
<td>0.00</td>
<td>3.17 ± 0.08</td>
</tr>
<tr>
<td>HF pre-device</td>
<td>5.11 ± 0.20*</td>
<td>26.1 ± 1.0*</td>
<td>33 ± 3*</td>
<td>0.33 ± 0.03*</td>
<td>3.75 ± 0.08*</td>
</tr>
<tr>
<td>HF + device × 4 weeks</td>
<td>5.31 ± 0.19</td>
<td>25.4 ± 2.0</td>
<td>30 ± 3</td>
<td>0.11 ± 0.04‡</td>
<td>3.37 ± 0.23‡</td>
</tr>
<tr>
<td>No device implanted (n = 3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.30 ± 0.20</td>
<td>19.8 ± 1.5</td>
<td>69 ± 1</td>
<td>0.00</td>
<td>2.82 ± 0.28</td>
</tr>
<tr>
<td>HF pre-device</td>
<td>5.38 ± 0.32*</td>
<td>26.2 ± 2.2*</td>
<td>33 ± 4*</td>
<td>0.40 ± 0.02*</td>
<td>3.50 ± 0.11*</td>
</tr>
<tr>
<td>HF + 4 weeks</td>
<td>5.49 ± 0.17</td>
<td>31.0 ± 4.0</td>
<td>28 ± 6</td>
<td>0.39 ± 0.05</td>
<td>3.73 ± 0.11</td>
</tr>
</tbody>
</table>

*p < 0.05 HF pre-device vs. baseline; †p < 0.05 HF + device × 4 weeks vs. HF pre-device; ‡p < 0.05 HF + device × 4 weeks vs. HF + 4 weeks. HF = heart failure; LVEDD = left ventricular end-diastolic dimension; LA = left atrial; MR = mitral regurgitation.
guide catheter. A CS venogram was performed to measure the length and width of CS, particularly at the sites that would interface with the proximal and distal device anchors. The CS venogram was repeated after device placement to exclude dissection/disruption of the CS. A measuring catheter was also introduced into CS to assist in device sizing. Coronary angiography was performed at baseline, intermittently during positioning of the device, and again after final placement.

The mitral annuloplasty device was selected after baseline measurements of the size of CS. With experience, use of marking catheters improved assessment of CS size in the HF dogs, and the range of device sizes needed on hand was more predictable. The device was advanced into the CS and the distal end was deployed at variable percentages (75% to 95%) of the distance between the CS and the anterior intraventricular vein. Transthoracic echocardiography was performed while putting tension at the distal end and pulling it in increments of 1 cm each (“cinching the device”). If traction failed to reduce MR jet area/LA area by ≥50%, the device was recaptured and a new device was placed with the distal anchor positioned further out in the CS and traction was reapplied assessing MR severity and coronary flow. If the MR was reduced by >50% and coronary flow was preserved, the proximal anchor was deployed and the device was uncoupled from the delivery system. After full device deployment, final assessments of MR severity (Doppler echocardiography and contrast ventriculography), coronary flow, CS venogram, and LV hemodynamics were performed. If LV systolic pressures were lower at the final MR assessment, phenylephrine was infused at a dose titrated to provide similar LV systolic pressures at the baseline and final studies. This was necessary in only one dog.

**ECHOCARDIOGRAPHY.** Transthoracic two-dimensional and color flow images were obtained as noted for Study 1. Additionally, during the placement of the device, the MR severity was assessed by the PISA method with calculation of the regurgitant volume and effective regurgitant orifice area (ERO). This assessment requires measurement of the
radius (cm) of the PISA in the LV, the aliasing velocity, and the velocity and time-velocity integral of the continuous-wave MR signal. The ERO and the regurgitant volume were then calculated using the standard formulas (9). As dogs are considerably smaller than humans, with smaller hearts and lower cardiac output, no criteria exist regarding the relationship of PISA values to severity of MR.

For echocardiographic measurements in conscious dogs, only the parasternal short- and long-axis views were possible with the dog standing, thus PISA assessment of MR was not possible. Two-dimensional guided M-mode measurements of LV end-diastolic and end-systolic dimension were made in the short-axis view and ejection fraction was calculated using the Teichholz formula. Two-dimensional measurements of the transverse annular dimension in the short-axis view and the long-axis view were made. The maximal MR jet area in the long-axis view and corresponding LA area were measured.

CONTRAST VENTRICULOGRAPHY. Mitral regurgitation severity was graded (0 to 4) using criteria similar to those used in humans. As blinding of the interpreter as to the presence or absence of the device was not possible, the interpreter graded the MR in the pre- and post-device ventriculograms in separate batches blinded to the identity of the dog and the previous or subsequent ventriculogram.

PATHOLOGY. Nine of the 12 hearts were available for pathologic examination with perfusion fixation in most. Hearts were sectioned and analyzed with an experienced cardiac pathologist (W.D.E.) paying particular attention to the relationship of the CS, circumflex coronary artery, and mitral annulus in the area of the distal CS, proximal circumflex, and distal anchor.

STATISTICAL ANALYSIS. Data were averaged and reported as mean ± SEM. Paired and unpaired t tests were used for statistical comparisons. A probability value of p < 0.05 was considered significant.

RESULTS

Study 1. PACING-INDUCED HF. The rapid pacing protocol resulted in LV dilation and severe systolic and diastolic dysfunction (Tables 1 and 2).

ACUTE EFFECT OF PERCUTANEOUS ANNULOPLASTY ON THE DEGREE OF MR AND HEMODYNAMICS IN THE ABSENCE AND PRESENCE OF PHENYLEPHRINE. Cinching the device resulted in a decrease in the mitral annulus diameter, the MR jet area, and the MR jet area/LA area ratio (Table 1, Fig. 2). There were no significant changes in LV pressures, volumes, and systolic or diastolic function (Table 1, Fig. 2). The LA pressure did not increase. Compared with the baseline state, phenylephrine infusion resulted in increases in peak LV systolic pressure, end-diastolic pressure, end-diastolic volume, positive dP/dt, and MR jet area/LA area ratio (Table 1, Figs. 2 and 3). There were no significant changes in the other parameters. During phenylephrine infusion, cinching the device resulted in small but statistically significant
decreases in LV stroke volume and ejection fraction while the mitral annulus diameter, MR jet area, and the MR jet area/LA area ratio decreased dramatically. The methodology we employed for calculating stroke volume (end-diastolic minus end-systolic volume) includes “forward” (effective) and regurgitant volume; therefore, the small decrease in stroke volume could be related to the observed decrease in MR.

**Study 2. Placement of the Device in Dogs with Experimental HF.** Four dogs were studied in phase 1 with the first prototype of the device. The anchors of this prototype were undersized; in two dogs, the device could not be placed as the anchors were too small to stabilize the device. In one dog, a suitable size was available and the acute and chronic effects were assessed. In the fourth dog, a suitable size was available, an acute effect was demonstrated, and the device was deployed. While preparing to perform coronary angiography after final device placement, the dog fibrillated presumably due to impingement on coronary flow but resuscitation was unsuccessful and documentation of circumflex occlusion was not possible. After this experiment, the protocol was altered to mandate repeated angiography during the positioning of the device, not just after final placement. Two dogs were studied in phase 2 (prototype 2) with successful device placement. Six dogs were studied in phase 3 (prototype 3) with device placement in four dogs and inability to implant a device due to coronary impingement in two (fatal in 1).

In 7 of the 12 dogs, the distal anchor was able to be deployed distally (at 75% to 95% of distance between CS os and anterior intraventricular vein) in the CS with acute efficacy and no impingement of coronary flow (Fig. 4D). Three patterns of the course of the CX and CS were noted. In four dogs, the proximal CX was on the annular or atrial side of the CS in the distal CS and crossed to the epicardial and sometimes then ventricular side of the CS over the
distal portion of the CS in the region where the distal anchor would be positioned (Fig. 4A). The two dogs with coronary impingement that had assessment of coronary anatomy had this general pattern (Figs. 5 and 6). In three dogs, the proximal CX was on the atrial or annular side of the CS in the distal CS and passed on the annular side of the CS to the ventricular side of the CS in the distal portion of the CS where the distal anchor would be positioned (Fig. 4B). In two dogs, the proximal CX was far down on the ventricular side of the CS and maintained this position throughout the distal CS (Fig. 4C).

In one dog, placement of the distal anchor at 90% resulted in impingement of CX flow (Fig. 5A). Placement of the device at 85% gave good efficacy with good CX flow (Fig. 5C). The delivery system was uncoupled and within minutes the dog developed ischemia and CX occlusion was documented. In retrospect, there was impingement on the CX, with the final device placement at 85% compared with the baseline angiogram (Fig. 5D) that was not appreciated at the time. This dog died and examination of the CX and CS anatomy in the harvested heart revealed that the proximal CX ran on the atrial side of the CS in the distal CS and then crossed over to the epicardial and then ventricular side of the CS (Fig. 5B) over the portion of the CS where the distal anchor was positioned. The proximity of the CX and distal CS in this dog may have increased the likelihood of compression of the CX with tension on the device. However, this anatomy was not too dissimilar to that observed in two other dogs in which no impingement of CX flow occurred.

In another dog, placement of the device at 85% did not impede coronary flow after deployment of the distal anchor (Fig. 6A, top), but did when tension was applied to cinch the device and reduce the mitral annulus (Fig. 6A, bottom). The device was repositioned at 75%, but this position limited flow with deployment of the distal anchor (Fig. 6C, left) and occluded flow with applying tension to cinch up the annulus (Fig. 6C, right). No device was placed, as less distal positions afforded unsatisfactory acute efficacy. The dog underwent four weeks’ additional pacing per protocol.
Examination of CX and CS anatomy after sacrifice revealed that the proximal CX ran on the annular side of the CS and then spiraled to the atrial, epicardial, and then ventricular side of the CS over the portion of the CS where the distal anchor was positioned.

Thus, 7 of 12 dogs had successful placement to assess acute and chronic efficacy, 3 of 12 had coronary anatomy that precluded efficacious placement of the device without ischemia, and 2 had failure to place the device because of early prototype design issues. No CS dissection or perforation was noted despite placement and repositioning of multiple devices in the CS in the final phase with the most mature prototype.

There was a clear relationship between the degree of annular diameter and MR reduction and the position of the distal anchor, with maximal results achieved with the most distal placement of the distal anchor. Further, the degree of annular diameter and MR reduction were related to the amount of tension (and thus deformation of the annulus) placed on the device before deployment of the proximal anchor. The length of the device is also an important consideration, and devices must be appropriately sized to insure that the entire device resides in the CS.

**ACUTE EFFECT ON MR.** Figure 7 demonstrates the acute effect of the device placement on MR severity as assessed by four separate indices with grouped data and representative examples of each index of MR severity in a single dog at baseline and after device placement. Left ventricular systolic pressure at the time of baseline and final assessment of MR were similar (105 ± 4 mm Hg vs. 106 ± 5 mm Hg, p = 0.96). There was a marked reduction in the MR jet area/LA area ratio. In one of the seven dogs that had successful placement of the device, the baseline PISA could not be performed for technical reasons. In two of the six dogs with baseline PISA measurements, the measurements could not be obtained after device placement because the residual MR was minimal and full development of the MR jet by continuous wave Doppler and/or the PISA radius was not possible. In the four dogs with paired data, the reduction in ERO and regurgitant volume was significant. By contrast ventriculography, the grade of MR was reduced.

**CHRONIC EFFECT ON MR.** The LV and LA size, ejection fraction, mitral annular dimension, and MR jet area/LA area ratio at baseline, after the induction of HF (HF-pre-device) and at four weeks (HF-4 weeks) after the device placement procedure (with continued rapid pacing) in surviving dogs who received a device (n = 7) and those who did not (n = 3) are shown in Table 2. The pacing protocol resulted in LV, LA, and mitral annular enlargement; systolic dysfunction; and moderate MR. These changes remained stable to more severe at four weeks in those dogs that did not receive a device. In dogs that received a device, mitral annular dimension and MR jet area to LA area were reduced compared with the HF-pre-device data.
DISCUSSION

We evaluated potential efficacy and safety of a percutaneous mitral annuloplasty device in a clinically relevant model of experimental HF due to rapid ventricular pacing. In the first study we performed, placement of a device in the CS with simulated deployment reduced mitral annulus diameter and severity of MR without deleterious hemodynamic effects or induction of mitral stenosis. In the second study, which more closely approximated the intended clinical scenario, PMA resulted in acute and chronic reduction of mitral annular diameter and MR severity. Several important observations regarding factors critical for efficacy (optimal placement of distal anchor, appropriate anchor size and device length, degree of tension needed before deployment) and safety (appreciation of the relationship between the CS and the circumflex coronary artery and ability to deploy and recapture device without CS dissection) were defined.

Functional MR becomes an increasing hemodynamic burden as LV remodeling progresses in patients with HF, and the interaction between the two processes generates a vicious cycle. In a broad spectrum of patients with acute myocardial infarction or with systolic dysfunction, the presence of MR is associated with worse outcomes (10,11). Although pharmacologic interventions have been shown to positively influence LV remodeling, advanced HF frequently develops despite maximal medical therapy. We have recently reported that functional MR is common in patients with advanced HF referred to a refractory HF clinic (12). Mitral annuloplasty is a promising therapy for patients with advanced HF and significant functional MR (2). Indeed, surgical techniques have improved, allowing surgical approaches to HF even in patients with severe systolic dysfunction, and there is considerable interest in newer surgical modalities to prevent the progression of or to reverse LV remodeling (13). However, 80% of patients with HF are >65 years of age and 50% are >80 years of age. The prevalence of significant renal dysfunction, one or more previous sternotomies, and other comorbidities in these elderly patients is high, and many patients with advanced HF and functional MR are not good surgical candidates. Additional therapeutic options for such patients are needed, and the promising results of surgical mitral annuloplasty in younger patients with HF suggest that PMA would be an effective HF therapy in those patients who are not candidates for surgical approaches.

The present study supports the concept that novel device therapy to reduce MR severity in HF may be feasible and effective. It also defines important factors needed for efficacy.
and potential limitations to this approach, most notably the relationship of the CS and circumflex coronary artery. We had speculated that if the CX ran between the CS and annulus for an extended distance, the risk for tension on the device to compromise flow would be greatest. However, the two instances of CX compromise did not clearly display this variant. Careful patient selection, device positioning, and sequential angiography during device placement will be needed in clinical studies in patients with a patent native CX.

The potential for PMA to widen the therapeutic armamentarium for advanced HF is very attractive. However, its potential applicability will need to be assessed on an individual basis, as the presence of active ischemia, an area of anterior akinesia, or severe tricuspid valve regurgitation could make a surgical approach more appealing in those who are otherwise surgical candidates. Concomitant severe tricuspid regurgitation and right HF may also limit clinical response to PMA.

**Study limitations.** The degree of MR associated with rapid pacing-induced LV dysfunction in the conscious dog was not severe. However, under anesthesia in the closed-chest dog, the severity of MR was more significant and the device markedly reduced the severity of MR. Indeed, elimination of milder MR may be more difficult than reduction of severe MR, as reduction in a less dilated annulus may distort leaflet coaptation. In sheep, targeted coronary ligation has been reported to produce severe MR (14), and such models could be studied as there is concern that mitral annuloplasty alone may not provide adequate or lasting reduction of MR in ischemic cardiomyopathy (15). However, in sheep the circumflex coronary artery does not run in the atrioventricular groove, limiting its suitability to assess safety issues. There are other factors unique to the human HF population that likely cannot be assessed in any animal model, and although these studies and others (16,17) have provided “proof of principle” and insight into technical considerations, ultimate clinical utility and safety can only be defined in humans.

**Conclusions.** This new percutaneous mitral annuloplasty device significantly reduced mitral annular dimension and the severity of functional MR associated with severe experimental HF in a species whose CX and CS anatomy are similar to humans with a left dominant circulation. The need for careful assessment of coronary anatomy during implantation is established. These data and the promising results obtained with surgical annuloplasty in advanced human HF associated with severe functional MR lend support for future clinical studies that would define the therapeutic potential and safety of such devices in human HF.

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**References**


