Conclusions—The percutaneous septal sinus shortening system is effective in ameliorating functional MR in an ovine model.

Methods and Results—Sheep underwent rapid right ventricular pacing to obtain moderate to severe functional MR with septal-to-lateral (SL) mitral annular enlargement. The percutaneous septal sinus shortening system was placed via standard interventional techniques consisting of a bridge (suture) element between interatrial septal wall and great cardiac vein anchors. Through progressive tensioning of the bridge element, direct SL shortening was achieved. Sheep underwent short-term (n=19) and long-term (n=4) evaluation after device implantation. In short-term studies, SL diameter decreased an average of 24% (32.5±3.5 to 24.6±2.4 mm; P<0.001), and MR grade significantly improved (2.1±0.6 to 0.4±0.4; P<0.001). Despite continued rapid pacing, chronic device implantation resulted in durable SL shortening (30.4±1.9 mm before implantation to 25.3±0.8 mm at 30 days; P=0.01) and MR reduction (1.8±0.5 before implantation to 0.2±0.1 at 30 days; P=0.01). Increased cardiac output, decreased wedge pressure, and decreased brain natriuretic peptide levels were observed in animals undergoing long-term device implantation.

Conclusions—The percutaneous septal sinus shortening system is effective in ameliorating functional MR in an ovine model. The procedure, which uses standard catheter techniques, can be deployed largely under fluoroscopic guidance. The unique bridge element appears durable and allows direct and precise SL shortening to a diameter optimal for MR reduction. (Circulation. 2006;113:2329-2334.)

Key Words: cardiomyopathy, catheters, echocardiography, mitral valve, regurgitation
proximal end of the lead was connected to a pacemaker (Kappa SR401, Medtronic, Minneapolis, Minn) positioned subcutaneously in the right supraclavicular fossa. Animals were paced at a rate of 180 bpm for 5 weeks, at which time screening transthoracic echocardiography was performed. Furosemide 25 mg and amiodarone 400 mg were administered enterally daily during the pre-device implantation pacing period. All animals were treated humanely in compliance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 82-83, revised 1996).

Echocardiography

After right ventricular pacing as described above, animals underwent left-sided transthoracic echocardiography (Acuson Cypress, Siemens, Malvern, Pa). Animals found to have (1) >15% MR/left atrial (LA) area at a systolic blood pressure >120 mm Hg, (2) ejection fraction >25% and <40%, (3) SL dimension >27 mm, and (4) septo–great cardiac vein (GCV) dimension >33 mm formed the study group. MR was assessed and quantified by an experienced echocardiographer (P.T.) as none (0), trace (0.25), mild (1), moderate (2), moderate to severe (3), and severe (4). In animals with sufficient MR to proceed with device implantation, intracardiac echocardiography (10F Acuson catheter) was performed from the ascending thoracic aorta before, during, and after device tensioning. Intracardiac echocardiography yielded a standard long-axis view whereby LA diameter, SL length, MR severity, and leaflet mobility could be assessed before and after device implantation. Some animals with sufficient MR underwent continued pacing and formed the control group.

Hemodynamic Assessment and Device Implantation

Before device implantation, animals were premedicated for 3 days with enteral clopidogrel (300 mg once, then 75 mg/d) and aspirin (325 mg/d). Dual antiplatelet therapy was continued until termination. Brain natriuretic peptide values were obtained before and after long-term chronic implantations. Preimplantation and terminal hemodynamic assessments were performed with measurement of pulmonary artery and pulmonary capillary wedge pressures and thermodilution cardiac outputs. Gentamicin and cefazolin were given intravenously immediately before the procedure, and oral cephalaxin was continued for 5 days after the procedure. At the start of the implantation procedure, 150 mg IV amiodarone was given over 1 to 2 hours, and the pacing rate was decreased to 110 bpm. Animals were anesthetized and intubated for the procedure, which was performed under fluoroscopic and intracardiac echocardiographic guidance. A 12F sheath was placed in the right internal jugular vein, a 12F sheath was placed in the right common femoral vein, and an 11F sheath was placed in the right common femoral artery. Heparin was given to maintain an activated clotting time >400 seconds. The coronary sinus and GCV were wired through the right internal jugular vein using a glide wire (Terumo Medical Corp, Somerset, NJ); the distal end of the wire was placed in the anterior interventricular vein. A coronary sinus venogram was performed to assess size and configuration of the GCV. In several cases, the ostium of the GCV was narrowed (Vieussens’ valve) and was predilated with a 6- or 7-mm-diameter balloon catheter. The GCV MagneCath, which incorporates a shaped permanent magnet on its distal tip, was then advanced into the GCV and positioned 4 to 5 cm proximal to the origin of the anterior interventricular vein, which resulted in a central position behind the posterior mitral leaflet. A transseptal puncture was performed using the standard technique (~15% of animals had a patent foramen ovale that was used), and a 12F Mullins catheter was placed in the left atrium through which the LA MagneCath, also incorporating a shaped permanent magnet on its distal tip, was then advanced into the GCV and positioned 4 to 5 cm proximal to the origin of the anterior interventricular vein. After the catheters were mated, a crossing catheter was advanced from the LA MagneCath into the GCV MagneCath, making a small 0.062-in hole in the LA wall. A glide wire was then passed from the left atrium into the coronary sinus and externalized as a continuous right common femoral vein–left internal jugular vein loop, and the MagneCaths were removed. The T-bar element was then advanced into the coronary sinus, and an attached suture (bridge element) was pulled back across the transseptal puncture using the “loop” glide wire and externalized at the right common femoral vein. The septal anchor (current prototype using a 35-mm Amplatzer patent foramen ovale occluder, Golden Valley, Minn) was then deployed over the suture element in a standard fashion, and tension was applied on the suture to effect SL shortening. Once the desired degree of shortening was
achieved, a suture lock was used to secure the final tension level. Through progressive tensioning of the bridge element, direct SL shortening was achieved with amelioration of FMR (Figure 1 and online Data Supplement). At the conclusion of the procedure, great cardiac venography and left coronary angiography were performed in all animals to assess patency. The pacing rate was increased to 180 bpm, and amiodarone was continued daily until termination.

Terminal Studies
At 30 days after implantation, animals were evaluated by echocardiography, and hemodynamic evaluation was repeated. Great cardiac venography and coronary arteriography also were repeated. Animals were euthanized after administration of 10,000 U heparin to eliminate postmortem clot from the device. After removal of the heart, the LA dome was incised, and the PS3 system and associated anatomic structures were examined. The heart was fixed in 10% formalin and submitted to histological examination.

Statistical Analyses
Statistical analyses were performed with the use of the Stata Intercooled statistical program (Stata Corp, College Station, Tex). All values are reported as mean±SD. For repeated measures before and after short-term implantation, a paired Student’s t test was used. For repeated measures in long-term studies, ANOVA was used. Values of \( P<0.05 \) were considered significant.

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

Results
The PS3 system can effectively ameliorate FMR in this ovine model. Sheep underwent short-term (n=19) and long-term (n=4) evaluation after device implantation. There were significant short-term reductions in the SL systolic dimension and MR grade that were sustained at 30 days (Table). The SL diastolic dimension was similarly reduced with PS3 implantation (data not shown), but this was thought to be less relevant because MR is a systolic phenomenon. In all short-term studies, there was no visible impingement on the circumflex coronary artery, and the GCV was patent after procedure in all animals. No significant atrial arrhythmias were noted. Only a modest tensioning force (\( \approx 147 \) g) was required to

Figure 2. Intracardiac echocardiography before and after PS3 system implantation. Note the improvement in MR from 3+ (left) to trace (right) after device implantation. Septal anchor is seen on the right (arrow).

Figure 3. Chronic PS3 system implantation results. A, SL systolic distance before implantation, immediately after implantation, and at 30 days. B, MR grade before implantation, immediately after implantation, and at 30 days. Results for PS3-implanted animals are in gray (n=4); controls are in black (n=2). See text for numerical details.
achieve adequate SL shortening as determined from prior investigation in an open-chest model. Representative echocardiographic images before and after PS3 implantation are shown in Figure 2. Although the 4 animals that underwent successful long-term (30-day) device implantation had sustained improvement in SL length and MR grade, the SL distance increased from 27.7 to 36.4 mm after continued pacing and MR worsened from 2.0 to 2.3 in 2 control animals (Figure 3). With the latest-generation device reported here, there was a high implantation success rate (>90%). Most procedural failures were due to hemodynamic instability/collapse of the cardiomyopathic animals during general anesthesia.

There was improvement in cardiac output and a significant decrease in pulmonary capillary wedge pressure in animals undergoing long-term device implantation. The cardiac output was 3.46±0.76 L/min before implantation and 3.69±0.0 0.77 L/min at 30 days ($P=NS$). The pulmonary capillary wedge pressure before implantation was 23.9±4.1 mm Hg and fell to 13.8±2.2 mm Hg at 30 days ($P=0.01$). Device implantation resulted in an improvement in brain natriuretic peptide levels from 20.0±9.1 ng/mL before to 13.3±4.5 ng/mL after implantation (Figure 4).

Gross pathology at 30 days demonstrated no device migration, erosion, or bridge thrombosis. Histological examination of the system elements showed appropriate fibrosis and endothelialization (Figure 5).

**Discussion**

The PS3 system is a novel percutaneous procedure that is effective in ameliorating FMR in this ovine tachycardia model. It is clear that percutaneous or other less invasive therapies are needed to address a population of individuals with FMR/IMR who are not ideal surgical candidates but who likely would benefit from a reduction in their MR.$^{11-13}$ Currently, multiple percutaneous approaches to treat MR are under development. These can be broadly categorized into leaflet (or “edge-to-edge”) approaches for patients with adequate leaflet proximity (and not generally with FMR/IMR),$^{14,15}$ coronary sinus “annuloplasty” approaches for the treatment of FMR or IMR,$^{16-20}$ direct annular plication approaches simulating a true

<table>
<thead>
<tr>
<th>SLS Before PS3, mm</th>
<th>SLS Short Term After PS3, mm</th>
<th>SLS Short-Term Reduction, %</th>
<th>SLS at 30 d After PS3, mm</th>
<th>MR Before PS3, mm</th>
<th>MR After PS3, mm</th>
<th>MR Reduction</th>
<th>MR at 30 d</th>
</tr>
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<tbody>
<tr>
<td>Short term (n=19)</td>
<td>32.5±3.5</td>
<td>24.6±2.4*</td>
<td>24±7</td>
<td>21±7</td>
<td>2.1±0.6</td>
<td>0.4±0.4*</td>
<td>1.7±0.6</td>
</tr>
<tr>
<td>Long term (n=4)</td>
<td>30.4±1.9</td>
<td>23.9±0.5†</td>
<td>21±7</td>
<td>25.3±0.8†</td>
<td>1.8±0.5</td>
<td>0.2±0.1†</td>
<td>1.6±0.6</td>
</tr>
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SLS indicates septal-lateral dimension in systole.

* $P<0.001$ vs before measurement; † $P=0.01$ vs before measurement; ‡ $P=NS$ vs after PS3.
surgical annuloplasty, and direct left ventricular remodeling using a transventricular device. The PS3 system represents a completely distinct percutaneous therapy for MR involving direct reduction of the SL dimension by means of a transatrial bridge. Prior pathophysiological studies have demonstrated that SL enlargement is the common final pathway in the development of FMR or IMR and that shortening this dimension is critical to alleviating MR. For instance, pure papillary muscle repositioning by means of a suture in an animal model of IMR mildly reduced the SL dimension but did not decrease MR, whereas suture-mediated SLAC reduced the SL dimension, corrected lateral posterior papillary muscle displacement, and decreased MR. Prior published work on coronary sinus annuloplasty devices has demonstrated variable efficacy in the ability to reduce the SL dimension (range, 10.1% to 23.7% reduction). Because direct SLAC has demonstrated that, on average, higher reductions in the SL dimension are required to ameliorate FMR (range, 18.7% to 28.1% reduction), one may therefore infer that a percutaneous approach that cannot reliably achieve this degree of shortening may be less efficacious.

In the surgical treatment of FMR/IMR, SL shortening is attained through the use of complete or partial annuloplasty rings that are firmly anchored to the left and right fibrous trigones. This anchoring provides the traction necessary to pull the posterior annulus anteriorly, invoking Newton’s third law, which states that for every force there must be an equal and opposite force. In the case of the coronary sinus annuloplasty devices, the force pushing the posterior annulus forward is counterbalanced by traction and/or outward force on the coronary sinus, often near the trigonal areas. Unfortunately, the left fibrous trigone is an area where the circumflex coronary artery frequently crosses the coronary sinus and would therefore theoretically move these devices more likely to cause circumflex coronary artery impingement. It has been published that up to 25% of attempts to place a coronary sinus annuloplasty device were not completed because of significant compression of the circumflex coronary artery. The PS3 system does not involve the trigonal areas, and circumflex coronary artery compression was not observed in any study.

The PS3 system provides the ability to directly “pull” the posterior annulus forward given its anchor points in the mid GCV and the interatrial septum. It is important to note that the mechanism by which the PS3 system results in SL shortening is deflection of LA tissue superior to the mitral annulus. The large radius of the right atrial disk (35 mm) of the septal anchor distributes force over a larger area and minimizes any tendency to herniate. In addition, the PS3 system allows precise millimeter-level adjustment of SL length to achieve optimal reduction in MR. Current coronary sinus annuloplasty systems may result in unpredictable shortening over time or a lack of fine tensioning control as a result of larger stepwise tensioning manipulations.

In regard to the bridge element spanning the left atrium, no thrombosis was seen in short- or long-term studies during dual antplatelet therapy, and histology showed appropriate endothelialization and fibrosis (Figure 5). Bridge thrombosis is not anticipated to be a major issue because numerous percutaneous patent foramen ovale and atrial-septal defect closure devices with considerable surface area in the left atrium have shown a very low rate of thrombosis if antiplatelet therapy is administered. Although there is tension on the PS3 system, it is modest (=147 g), and histology has shown reactive fibrosis around the anchor points that may lead to additional integrity of these points. It should be noted that tension is a common feature of all percutaneous approaches, including edge-to-edge repair, and the long-term sequelae of this remain to be seen.

In summary, the PS3 technique has several potential advantages over existing percutaneous methods: (1) direct SL shortening with millimeter-level accuracy; (2) the ability to enter the GCV at variable locations to optimize reduction in MR that may be noncentral; (3) the ability to treat FMR/IMR; and (4) the use of standard catheter techniques and deployment largely under fluoroscopic guidance. Unlike surgical annuloplasty, posterior leaflet mobility appears unaffected with the PS3 system. A potential limitation of the system is that, unlike SLAC, the angle of the bridge element is ~20° to 30° posterior to a true anteroposterior orientation. However, ischemic MR often results in asymmetrical annular dilation, primarily of the posteromedial annulus. The posterior bridge angle of the PS3 system would theoretically address this asymmetrical annular dilation. It has been demonstrated that asymmetrical anterior or posterior commissural cinching in an ovine model also can reduce IMR.

Disclosures

Drs Rogers, Palacios, and Low are consultants to Ample Medical, Inc. Drs Macoviak and Rahdert have founding equity in Ample Medical, Inc. Dr Takeda reports no conflicts.

References


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**CLINICAL PERSPECTIVE**

Congestive heart failure resulting from systolic dysfunction is prevalent and often associated with functional mitral regurgitation (FMR) or ischemic mitral regurgitation (IMR). FMR arises from a failure of mitral leaflet coaptation despite normal leaflet motion; IMR stems from posteromedial papillary muscle displacement with restricted leaflet motion caused by tethering. Unfortunately, medical therapy for these conditions remains suboptimal, and surgical therapy carries attendant morbidity and mortality. Minimally invasive or percutaneous approaches under development include clip- or suture-mediated leaflet edge-to-edge repair and various devices that occupy and modify the shape of the coronary sinus. However, it is likely that not all causes of MR will be addressed by these 2 approaches. Prior research has demonstrated that the septal-to-lateral (SL, or anteroposterior) mitral annular diameter is increased in animal models of FMR and IMR and that direct SL annular cinching by means of a surgically placed suture can ameliorate the MR. This technique directly mirrors the change in mitral annular shape (reduced SL dimension) achieved by annuloplasty rings. We have developed a novel percutaneous technique, the percutaneous septal sinus shortening system, that mimics SL annular cinching and is demonstrated here to ameliorate FMR in an ovine model. The procedure incorporates standard catheter techniques and can be performed largely under fluoroscopic guidance.
Percutaneous Septal Sinus Shortening: A Novel Procedure for the Treatment of Functional Mitral Regurgitation

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