A Novel Method of Percutaneous Mitral Valve Repair for Ischemic Mitral Regurgitation

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Objectives This investigation sought to determine the feasibility of a novel method of a percutaneous mitral valve repair.

Background Percutaneous mitral valve repair has emerged as an alternative therapy for patients with functional mitral regurgitation. However, current methods that rely on cannulation of the coronary sinus may not result in direct reduction of the mitral annulus area due to the superior relationship of the sinus to the annulus.

Methods A novel device, consisting of helical stainless steel screws connected by a biocompatible tether, was designed for percutaneous mitral valve repair. This device was implanted by implanting the helical screws directly into the myocardium at the posteromedial mitral annulus of 8 anesthetized pigs from the right internal jugular vein.

Results Implantation of the device resulted in a 19.7 ± 0.1% reduction in mitral annular area and an 18.8 ± 0.1% decrease in the mitral anterior-posterior dimension (both p < 0.05 vs. baseline). This annular reduction persisted at 3-month follow-up. Both the coronary sinus and left circumflex coronary artery remained patent in all animals. There was no evidence of device migration, poor wound healing, or tissue thrombosis at the sites of device implantation.

Conclusions Percutaneous mitral valve repair targeting the ventricular myocardium from central venous access is feasible. By directly acting on the posteromedial mitral annulus, this methodology targets the mitral annular area most frequently affected by ischemic mitral regurgitation, lessens the risk of coronary artery impingement, promotes coronary sinus patency, and overcomes technical concerns that may arise when the coronary sinus lies significantly superior to the mitral annulus. (J Am Coll Cardiol Intv 2008;1:663–72) © 2008 by the American College of Cardiology Foundation
Mitral regurgitation (MR) following myocardial infarction is a complex phenomenon, which arises from an interplay of annular dilation, ventricular remodeling, and geometric alterations of the mitral valve apparatus (1–5). Its occurrence carries significant morbidity due to progressive heart failure and a worse prognosis even when the regurgitation is mild or without symptoms (6–8). In an attempt to impact the clinical consequences of ischemic MR, conventional treatments have included surgical annuloplasty or, for those with severe distortion of the mitral valve apparatus, mitral valve replacement (9–15). These treatments have been largely undertaken in the context of need for open surgical revascularization, but also have been performed independently in selected patients (16–19). In these instances, early repair is favored with the goal of interrupting the cycle of heart failure due to progressive MR (20–23).

Over the past several years, percutaneous mitral annuloplasty for the treatment of functional MR has emerged (24–29). In comparison with open surgery, percutaneous annuloplasty has enormous appeal because of the potential to relieve MR and heart failure with relatively less invasive means. Amelioration of the risk of open heart surgery is particularly important for patients with functional MR, as these patients frequently have severe comorbidities that increase the risk of open surgical repair.

The present methods of percutaneous mitral annuloplasty have centered on reduction of the valve orifice via the coronary sinus. Nevertheless, there are limitations with the current techniques of percutaneous mitral annuloplasty. In many patients, the coronary sinus lies significantly superior to the plane of the mitral annulus, particularly near the medial aspects of the mitral annulus (30–32). In these instances, percutaneous coronary sinus reduction may result in traction on the left atrial wall with relatively less impact on true mitral annular reduction. This loss of efficacy may be particularly relevant for treatment of ischemic MR, where regurgitation more frequently affects the posteromedial portion of the mitral annulus (i.e., P2 and P3 leaflet segments) (33,33,34). In addition, in the lateral aspects of the mitral annulus, the anatomic course of the coronary sinus becomes more closely apposed to the left circumflex coronary artery (30,31). Because of this anatomic relationship, positioning of percutaneous devices deep (i.e., lateral) within the coronary sinus carries the potential for coronary artery impingement with device deployment (25).

Accordingly, this investigation was undertaken to evaluate the feasibility of a different percutaneous approach for mitral valve repair. In the present study, we describe a novel percutaneous method in which an annulus reduction device is implanted into the myocardium at the posteromedial mitral annulus. This method thereby specifically targets treatment of the mitral annulus affected by ischemic MR while lessening the risk of lateral coronary occlusion.

Methods

Percutaneous mitral annuloplasty device. The percutaneous mitral valve repair (PMVR) device is designed to reduce the area of the valve annulus in a manner analogous to open surgical ring annuloplasty. The PMVR device consists of 4 helical anchors (diameter × length, 2.5 mm × 10 mm), 2 loading spacers, a tether rope, and a locking mechanism (Fig. 1). Using endovascular techniques, the implant system is delivered to the mitral annulus via the coronary sinus and right atrium through the use of multiple dedicated 10- to 12-F delivery catheters (Figs. 2 and 3). The proximal pair of anchors is first implanted into the ventricular myocardium near the P2 segment of the mitral leaflet from the coronary sinus (Fig. 3). The proximal pair of anchors subsequently is implanted near the posteromedial trigone at the coronary sinus from the right atrium. Between these 2 pairs of anchors, a connecting polyurethane tether is used to shorten the annular distance, thereby effecting favorable change in mitral annular geometry (Fig. 4). Dynamic shortening of mitral annular distance can be performed manually and reversibly to ascertain the degree of reduction in regurgitation and untoward effects on the coronary sinus or adjacent coronary arteries (e.g., acute occlusion). The final locking mechanism of the PMVR device is a self-retracting, nitinol structure that maintains the cinched load.

Animals. This study was approved by the local Animal Care and Use Committee. All device implantations were performed at Advanced Preclinical Services (Coon Rapids, Minnesota) by the study authors. Eleven Yucatan pigs (weight 80.2 to 90.4 kg) were chosen for use in the present study to help approximate human size and minimize the impact of animal growth during follow-up. This animal model also was chosen for its characteristic proximal coronary sinus anatomy, in which the sinus typically lies superior to the mitral valve annulus and therefore represents a worst-case challenge for the translation of the technology to human application. Nevertheless, 2 anatomical features of this model presented significant challenges to proper PMVR device implantation: 1) drainage of a large persistent vena cava directly into the coronary sinus; and 2) small diameter of the coronary sinus distal to this vena cava (Fig. 4). Because of the large size and location of the persistent vena cava, implantation of the first set of anchors (distal pair) could only be performed in the coronary sinus in positions lateral to the vena cava. In this device location, the diameter of the coronary sinus is relatively small and would not accommodate the size of the delivery catheters in some
instances. The distal end of the delivery catheter when it is fully articulated is appropriate for the size of the lateral coronary sinus in humans (8 to 12 mm) (31–35).

**Procedures.** All studies were performed with animals in the fasting state. Each animal received prophylactic aspirin (325 mg daily) beginning 3 days before implantation that was continued throughout the study. All animals also received intravenous lidocaine (1 mg/kg bolus and 1 mg/kg/h drip) at procedure initiation. Following general anesthesia, mechanical ventilation was maintained on a fraction of inspired oxygen of 40%. Venous access for PMVR device implantation and for intracardiac echocardiography (ICE) was obtained through sterile surgical cutdown of both the left and right internal jugular veins and placement of an 14-F vascular sheath. Arterial access for coronary angiography and pressure monitoring was obtained by similar sterile surgical cutdown of either the carotid or femoral artery and placement of an 8-F vascular sheath. Unfractionated heparin was administered to maintain an activated clotting time >200 s during the procedure.

Before PMVR implantation, angiography of the coronary sinus and adjacent venous structures was performed to define the venous anatomy and proximity of the major

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**Figure 1. PMVR Device**

(A) Side view of PMVR device showing 4 helical stainless steel screw anchors connected by a biocompatible tether. (B) Top view of PMVR device. (C,D) Guide catheter for implantation of the anchors into the mitral annulus. The distal end of the guide catheter can be articulated up to 90° to enable back wall support from the coronary sinus and directionality for device implantation. ICE — intracardiac echocardiography; LV — left ventricle; PMVR — percutaneous mitral valve repair.

**Figure 2. Cross-Sectional View of the Implanted PMVR Anchor**

Each anchor is implanted from the coronary sinus or right atrium into the ventricular myocardium at the level of the mitral annulus. Abbreviation as in Figure 1.
epicardial coronary arteries (Fig. 5). Following anatomical mapping, a 0.035-inch J-tipped guidewire is advanced into the distal (i.e., lateral) coronary sinus or 1 of its major branches. The delivery catheter is advanced into the distal coronary sinus over this wire, followed by removal of the guidewire. The delivery catheter contains a flexible, steerable distal segment that can be articulated to 90° (Fig. 1). This articulation enables back wall support from the coronary sinus during anchor implantation and accurate positioning of the anchors directly toward the mitral annulus. Following articulation and positioning of the delivery catheter near the P₂ segment of the mitral valve, the anchors are driven into the ventricular myocardium by counterclockwise rotation of a separate deployment tool within the delivery catheter that is coupled to the anchors. This deployment is reversible for the first 2 turns until barbs protrude, after which the anchoring becomes permanent. Before placement of the proximal set of anchors, a polyester strain-relief covering is advanced over the tether to distribute the force from anchors like a pledget in the coronary sinus. Subsequently, in methods analogous to placement of the distal anchor pair, separate delivery catheters with articulating heads are used to place the third and fourth anchors immediately near the coronary sinus into the posteromedial trigone from the right atrium. Following deployment of both anchor pairs, a cincher catheter is advanced over the tether to enable dynamic manual cinching. This reversible maneuver allows evaluation of both the degree of cinching...
needed to result in effective mitral annular reduction and to detect impingement of epicardial coronary arteries before permanent anchor cinching. Once a safe and satisfactory level of annular reduction is achieved, the cincher catheter is tightened in the shortened configuration, followed by cutting of the tether by a dedicated cutter catheter, resulting in decoupling of the anchor set from the delivery system. Repeat angiography of the coronary venous system and both arteries was performed for assessment of vascular patency.

**Evaluation of mitral annular reduction.** Measurements of mitral valve annular area, mitral annular anterior-posterior (A-P) dimension (also known as the septal-lateral diameter), mitral valve commissure to commissure (C-C) dimension, left ventricular outflow tract diameter, and left ventricular end-diastolic diameter were performed with ICE immediately prior to and following PMVR implantation (Fig. 6). Intracardiac echocardiography was used because of poor echocardiographic windows from both transthoracic and transesophageal imaging in these animals. Imaging of the mitral valve with ICE was obtained with both long- and short-axis views similar to the standard acquisition planes used in conventional transthoracic echocardiography. End-expiratory digital records (average of 3 to 5 samples) of left ventricular end-diastolic pressure and pulmonary capillary wedge pressure were obtained with standard, calibrated fluid-filled catheters. Assessment of the same parameters of mitral valve geometry with ICE, hemodynamic evaluations, and angiography were repeated at 30 and 90 days following PMVR device implantation, followed by animal sacrifice. Adverse events in the periprocedural and follow-up were recorded, including occurrence of pericardial effusion or tamponade, atrial or ventricular arrhythmias (tachycardia or fibrillation), and development of atrioventricular block.

**Gross pathology and histology.** Following animal sacrifice, all hearts were explanted and grossly evaluated for adverse events, including device erosion, infection, bleeding, tricuspid leaflet impingement, arterial occlusion, and thrombosis. Following gross examination, the hearts were pressure-perfused with >200 ml of lactated ringers’ solution at 80 to
120 mm Hg. Pressure fixation of the heart was performed overnight using 10% neutral buffered formalin at 80 to 120 mm Hg. Radiographs of fixed, intact hearts in 2 orthogonal views were obtained. The right atrium and coronary sinus were incised to enable direct inspection of the PMVR device. Tissue surrounding the PMVR device was trimmed, and the section was grossly examined, photographed, radiographed, and then processed and embedded in methyl-methacrylate. Sections were prepared using EXAKT System (EXAKT Technologies, Oklahoma City, Oklahoma) and slides were stained with hematoxylin and eosin. Histological assessment of the device was performed to evaluate the implant site to assess implant integrity, inflammation, and appearance of fibrous tissue.

**Data analysis.** Comparisons of continuous variables were made with the appropriate 2-sample test: a 2-sample $t$ test in cases where the variable distributions were symmetric and a Wilcoxon rank sum test otherwise. To adjust for animal growth during follow-up evaluations, indexing was performed by dividing echocardiographic parameters by body weight. Unless otherwise noted, continuous variables are reported as mean ± SD. Statistical significance was set a priori at $p < 0.05$.

**Results**

**Procedures.** Eleven Yucatan pigs were anesthetized for implantation of the PMVR device. In 2 animals, the distal coronary sinus was too small to accommodate the articulating sheath of the PMVR device. In a third animal, the landing zone between the persistent vena cava and circumflex artery was too short, prohibiting device implantation in the sinus without circumflex impingement. Among the 8 animals that underwent PMVR device implantation, each implant was performed successfully without mechanical complications, conduction abnormalities, cardiac arrest, loss of coronary sinus patency, or coronary artery impingement. There also were no significant changes in left ventricular end-diastolic pressure during follow-up (16.6 ± 5.3 mm Hg vs. 18.3 ± 5.1 mm Hg; 90 day vs. baseline; $p = 0.5$).

**Mitral annular area reduction.** In each animal, acute implantation of the PMVR device led to an immediate reduction in the mitral annular area and A-P dimension ($p < 0.05$ for all paired comparisons) (Fig. 7). Overall, PMVR implantation acutely resulted in a 19.7 ± 0.1% reduction in mitral valve annular area ($p = 0.0003$ vs. baseline) and an 18.8 ± 0.1% decrease in the A-P dimension ($p = 0.0001$ vs. baseline), although the C-C dimension remained unchanged ($p = 0.19$ vs. baseline).

During follow-up, there was a significant increase in mean animal weight (90-day weight vs. baseline; 95.7 ± 5.8 vs. 84.1 ± 5.1 kg; $p = 0.0001$). The immediate reductions in mitral valve annular area and A-P dimension were maintained at 30 and 90 days (Fig. 7). The C-C dimension also was lower at both 30 days and at 90 days in comparison with baseline.

**Gross pathology and histology.** In all animals, angiography demonstrated the coronary sinus and left circumflex artery to be patent at 30 and 90 days. In all instances, the PMVR anchors had traversed the coronary sinus wall into the ventricular myocardium at the level of the mitral annulus.
Gross examination at 90 days demonstrated healed tissue surrounding the implanted anchors and connecting tether (Fig. 8). There was no evidence of device migration, tissue erosion, or thrombosis either localized to or remote from the device implantation (Fig. 8). Histology confirmed no migration of the implanted anchors. Small areas of dense infiltrations of macrophages surrounded by mature, fibrous connective tissue coverage were present on histology of the individual components (Fig. 8).

Discussion

Percutaneous mitral annuloplasty has emerged as a potentially less invasive therapy for relief of MR and heart failure. This innovative technology carries enormous therapeutic potential given the incidence of myocardial infarction (900,000 hospitalizations per year), the high prevalence of moderate or severe MR in these patients (>12%), and the poorer prognosis of these patients following onset of MR (36–38). The successful development of an effective, durable percutaneous method of mitral annular reduction would provide symptom relief and potentially interrupt the deleterious cycle of ventricular remodeling that can occur in these patients (23).

The present study demonstrates the feasibility of a novel method for percutaneous mitral annuloplasty. The principal advantage of this technology is the direct implantation of an annulus reduction device into the myocardium at the posteromedial mitral annulus. The present methodology helps to overcome circumstances in which the coronary sinus lies significantly superior to the plane of the mitral annulus. In a recent study of patients with significant MR (32), the minimum distance from the coronary sinus to the mitral annulus averaged $7.3 \pm 3.9$ mm along the entire length of the coronary sinus and was even greater ($9.3 \pm 1.0$ mm) at the proximal sinus. These distances may be larger in patients with severe MR (32). Because of this superior position of the sinus relative to the mitral annulus, cinching of the coronary sinus using some current devices may lead to cinching of the left atrial wall without true reduction in the mitral annular area (i.e., supravalvular stenosis). Variation of the distance from the coronary sinus to the mitral annulus poses a challenge to percutaneous approaches from the coronary sinus (32). The length (10 mm) of the anchors in the present methodology facilitated their implantation into the myocardium from the sinus, but can be elongated in future applications. Furthermore, the proximal anchor set is

![Figure 8. Gross and Microscopic Pathology After Device Implantation](image-url)
implanted directly into the posteromedial trigone. In the animal model of the present investigation, the anatomic relation of the coronary sinus is similar to that found in humans, and reduction of the valve orifice area was achieved by direct device implantation from the coronary sinus into the mitral annulus.

The present methodology was designed to solely target the posteromedial aspect of the mitral annulus for several reasons. First, the posteromedial aspect is the most frequently distorted portion of the annulus in patients with functional ischemic MR (3,33,34). Surgical treatment with the aim of correcting this asymmetry has been successful in these patients (e.g., Kaye annuloplasty). Second, targeting of the posteromedial aspect helps to avoid impingement of the left circumflex coronary artery following device deployment. In the lateral aspects of the mitral annulus (i.e., near P1 segment of the mitral valve), the course of the circumflex artery becomes more intimately related to the coronary sinus. This anatomic relation can be problematic for devices that implant in the lateral mitral annulus because the circumflex artery lies inferior or between the sinus and mitral annulus in the majority (>64%) of patients (30–32). Importantly, although the present methodology acts regionally, there was a significant, ~20% reduction in both the A-P (or septal-lateral) mitral annular diameter and in the overall mitral annular area. In the present study, the reductions in the A-P annular diameter and the overall mitral annular area by percutaneous annuloplasty are comparable to the results achieved with open surgical repair (39–41).

A major technical challenge to the present methodology is accurate positioning of each of the 4 helical anchors. The long axis of these anchors needs to be directed apically with minimization of their exposure to the pericardial space. Correct placement of the device will be challenging in patients with a coronary sinus that is either very large or too small, leading to ineffective back wall support of the articulated delivery catheter. Incorrect placement will result in cardiac perforation and potentially tamponade, which may also occur in patients with a very large distance of the coronary sinus to the mitral annulus. Of further note, implantation of the proximal anchor set also occurs near the atrioventricular node, which could result in complete heart block. Each step during percutaneous device insertion, including manual reduction of the mitral annulus, is completely reversible until the manual reduction is locked. This allows ongoing assessment of coronary artery patency and the effect on mitral regurgitation before final deployment. However, injury to surrounding structures during initial device deployment may still occur. Gross examination and histology demonstrated the implantation sites to be well healed 3 months after device deployment. Preservation of coronary sinus patency and the low profile of the device also allow future use of the sinus as may be needed in the management of these patients (e.g., biventricular pacing).

The absence of a reproducible animal model of ischemic mitral regurgitation has been a challenge in animal studies of percutaneous mitral annuloplasty. In some studies, induction of myocardial infarction using both percutaneous (i.e., coronary artery balloon occlusion) and surgical (i.e., coronary artery ligation) methods has been used (24,28). In our attempts, we were able to create and successfully eliminate ischemic MR with device implantation in 1 animal (Fig. 9). However, in our own experience and that of other investigators, few animals (<25% to 40%) survive these procedures and develop significant ischemic MR (28,42). Continuous rapid ventricular pacing, which has
been used by other investigators, has been shown to cause ventricular dilation and MR (24,25). Its major limitation is the reliance on global myocardial stunning without regional infarction and may not mimic the hemodynamic or morphologic milieu of patients with ischemic MR. In the present study, Yucatan pigs were selected for similarities to human heart size, the large diameter of the coronary sinus (also similar to humans), and the significant distance between the sinus and the mitral annulus. Although the effect on MR was not specifically evaluated, the similarities in size to human hearts and the significant distance between the sinus and mitral annulus allowed vigorous testing of the ability to implant into the mitral annulus from the coronary sinus and right atrium.

Functional ischemic MR occurs in 10% to 50% of patients with myocardial infarction and is associated with a poorer prognosis even when the degree of regurgitation is mild (6,42). Despite aggressive medical therapy, advanced heart failure frequently ensues in these patients. It is important to note that the present methodology does not directly address impaired ventricular function and dilation that are fundamental to the development of functional MR. Further ventricular remodeling may result in persistent or recurrent MR. Failure to address such remodeling has been a criticism of sinus-based percutaneous approaches (43). Nonetheless, we demonstrate reduction of the A-P (or septal-lateral) dimension of the mitral annulus with the present methodology, and such reduction alone has been found to be effective in abolishing chronic ischemic MR (42). Given the heightened mortality of current surgical operations for ischemic MR, the ability to repair MR percutaneously has inherent appeal. Should durable clinical efficacy of the present approach be demonstrated with further investigation, we believe this methodology will have a significant role in the armamentarium of therapies for patients with symptomatic functional ischemic MR.

Conclusions

Percutaneous mitral valve repair with device implantation into the ventricular myocardium at the mitral annulus is feasible. With this novel percutaneous method, reduction in mitral annular diameter may be accomplished with a lessened risk of circumflex artery impingement, preservation of coronary sinus patency, and overcoming the technical limitations posed when the coronary sinus lies significantly superior to the plane of the mitral annulus.

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