Endovascular Edge-to-Edge Mitral Valve Repair
Short-Term Results in a Porcine Model

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Background—The edge-to-edge technique is an accepted method for the surgical repair of a regurgitant mitral valve. This study reports the initial use of an endovascular technology that enables a double-orifice edge-to-edge mitral valve repair without cardiopulmonary bypass in an animal model.

Methods and Results—Adult pigs (n=14) were anesthetized, and left thoracotomy was performed for epicardial echo imaging. Using femoral vein access, a steerable guide catheter was placed transseptally into the left atrium. An implantable clip designed to grasp and approximate the middle scallops of the anterior and posterior mitral leaflets was introduced through the guide catheter. The clip was opened in the left atrium, advanced through the mitral orifice, and retracted to grasp the leaflet edges. When a functional double-orifice valve was confirmed by echo, the clip was closed to coapt the leaflets and detached from the delivery catheter. Before final clip detachment, echo demonstrated a double orifice in all 14 animals. In 2 studies, the clip released from the anterior mitral leaflet. Retrospective analysis of echo images indicated an incomplete grasp of the anterior leaflet. Immediate postmortem examination revealed that the clip successfully approximated the middle scallops of the anterior and posterior leaflets in all 12 double-orifice studies. Conclusion—This study demonstrates for the first time that an endovascular system can be successfully used to perform the edge-to-edge repair technique in a nondiseased porcine model. This technique is potentially applicable as a percutaneous catheterization laboratory procedure for the treatment of mitral regurgitation in humans. (Circulation. 2003;108:1990-1993.)

Key Words: mitral valve ■ regurgitation ■ catheterization

Repair of the mitral valve has become the preferred approach for the surgical management of mitral regurgitation (MR). Patients undergoing mitral valve repair have consistently demonstrated improved short- and long-term outcomes when compared with patients who receive a mitral valve prosthesis. Despite these favorable results, mitral valve repair is performed in only 35% of patients undergoing mitral valve surgical intervention. Valve replacement instead of repair is done primarily because of anatomic limitations, including leaflet pathology and/or a severely calcified annulus, which increase procedural complexity and compromise the outcome when repair is attempted. To expand the number of potential candidates for repair, surgeons have been investigating techniques that include chordal shortening and transposition, sliding leaflets, and the edge-to-edge or Alfieri technique. First used in 1991, the edge-to-edge approach involves approximating the middle scallops of the anterior and posterior leaflets with a suture, creating a so-called double-orifice mitral valve. (Figure 1). The clinical success and elegant simplicity of this technique prompted the development of a catheter-based, endovascular technology that is used to create a double-orifice mitral valve repair without cardiopulmonary bypass. The present study reports the initial results of this technology in a short-term animal model.

Methods

Device Overview
The endovascular cardiovascular valve repair system (CVRS, Evalve) consists of a 24F steerable guide catheter with a 22F distal end that is introduced through the femoral vein and placed across the atrial septum using standard transseptal techniques. The distal tip of the guide catheter has a bidirectional steering mechanism. Once in the left atrium, the tip of the guide is centrally positioned above the mitral valve using torque and handle-steering maneuvers. A “V”-shaped clip attached to a delivery catheter is then introduced through
shown in the open position. The 2 arms of the clip are opened in the left atrium once the clip is aligned with the long axis of the heart. Under echo guidance, the arms are rotated until they are perpendicular to the line of leaflet coaptation. The open, aligned clip is advanced across the mitral orifice and then retracted during systole (Figure 2). The clip arms are closed and locked when a double orifice has been created and confirmed by echocardiography. If needed, the clip can be reopened and repositioned. Opening, closing, locking, and detaching the clip are all controlled by the delivery catheter handle mechanisms. Once a functional double orifice has been created, the clip is detached from the delivery system.

Evalve Clip

The Evalve Clip is a 2-armed, soft tissue approximation device that when closed, has an outside diameter of 15 F, and when open, has a grasping span of 20 mm. It is designed to vertically coapt up to 8 mm of leaflet height specifically to replicate the Alfieri surgical approach with regard to width and length of tissue apposition. It is constructed of implant-grade metals and covered with polyester (Figure 2). The clip is designed to promote leaflet-to-leaflet healing around and into the device to maintain a point of permanent leaflet approximation.

Investigational Protocol

Fourteen consecutive studies in pigs ranging in weight from 101 to 135 kg are reported. A committee on animal research approved the protocol, and animals received humane care in compliance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

After premedication with ketamine and atropine, endotracheal intubation was performed and general anesthesia achieved with isoflurane. The animal was positioned on the angiography suite table in the right lateral decubitus position. An 18-gauge angiocatheter was placed in the left femoral artery for continuous hemodynamic monitoring. The right femoral vein was exposed by surgical cut-down. Left thoracotomy was performed, the left fifth rib removed, and the pericardium retracted to allow for direct epicardial echocardiographic imaging. A baseline echo study was performed (5- to 7-MHz probe) with collection of 2-dimensional and Doppler data in the standard views, including the short- and long-axis and reverse apical 2- and 4-chamber views imaged through the dome of the atrium. Heparin was administered to maintain an activated clotting time of >600 seconds. A catheter was passed into the right atrium through a longitudinal incision in the femoral vein, and transseptal access was obtained using standard techniques. The steerable guide catheter and dilator were advanced over a soft-tipped 0.35 guidewire, and the tip of the guide was placed 2 cm into the left atrium using a combination of fluoroscopic and echocardiographic guidance. The dilator and wire were subsequently removed. The steerable guide catheter was then positioned so that the distal tip was centered over the mitral valve line of coaptation, with 20 to 24 mm of height above the plane of the mitral annulus. The clip delivery catheter was then introduced through the guide catheter.

Evalve Clip Delivery Protocol

The clip was advanced out the end of the guide catheter under fluoroscopic guidance. In a long-axis echo view, the distal tip of the clip was positioned 1–2 cm above the mitral valve and the arms opened with the handle control mechanisms. The clip was then rotated in the short-axis view until the arms were perpendicular to the line of leaflet coaptation and the tip of the clip was above the desired point of coaptation of the middle scallops of the anterior and posterior leaflets (Figure 2). With the delivery catheter aligned with the long axis of the ventricle, the clip was advanced without rotation through the mitral orifice to a level just below the free edges of the leaflets. Leaflets were grasped by clip retraction against the leaflets timed to occur during systole. A thorough 2-dimensional and color Doppler echocardiographic evaluation was performed to confirm success of the grasp, including location of the clip, depth of tissue insertion within the clip arms, and absence of mitral insufficiency. If the result was deemed suboptimal, the clip was opened, advanced into the ventricle, and additional grasps were attempted. If major repositioning was indicated, the clip arms were inverted and the clip retracted into the atrium, where manipulations and adjustments could be performed distant from the chordae tendineae.

Once a successful grasp was confirmed, the clip arms were closed under fluoroscopic guidance. Further echocardiographic evaluation was performed to confirm successful creation of a functional double orifice. Until the final detachment steps, tissue could be released and the clip removed.

Evaluation Protocol

After the guide and delivery catheters were withdrawn, a detailed 2-dimensional and Doppler echocardiographic examination was performed. The animal was then euthanized according to the protocol. At postmortem, the left atrium was opened and the mitral valve inspected for evaluation of clip placement. The atrial and ventricular chambers and the inferior vena cava were exposed to look for catheter- or clip-induced damage. The valve was subsequently
excised for a more detailed inspection of clip placement and any possible trauma.

**Results**

Preintervention echocardiography demonstrated no significant mitral valve pathology or regurgitation. Transseptal puncture was successfully performed in all animals. Manipulation and steering of the catheter system in the left atrium allowed for precise positioning of the clip above the line of coaptation. The clip was opened in the left atrium and oriented appropriately in all 14 studies. The creation of a double orifice with central placement of the clip was prospectively confirmed in all animals. In 8 pigs, a double orifice was obtained with a single grasp; 4 animals required a second grasp, primarily as a result of inadequate initial leaflet approximation. One animal required 3 attempts, and 1 required 5 attempts. Three animals required the clip arms to be inverted and the system to be retracted back into the left atrium for repositioning.

After the clip was closed, echocardiography confirmed a functional double orifice without evidence of MR in all 14 pigs. After completely detaching the clip from the delivery catheter, a detailed echocardiographic study confirmed a functional double-orifice valve in 12 animals (Figures 3 and 4). Left ventricular fractional shortening remained normal, and there was no Doppler evidence of mitral stenosis or regurgitation. No hemodynamic instability was encountered during clip deployment in any of the studies.

In 2 animals, once the clip was released from the delivery catheter, it was noted that the clip was no longer attached to the anterior leaflet. On retrospective analysis of the fluoroscopic and echocardiographic images, it was observed that in both studies, the clip arms had not been fully opened to the correct position before grasping, and the partial grasp could be appreciated echocardiographically before detachment.

Duration of the studies, once transseptal access had been obtained, ranged from 45 to 90 minutes. Subsequent postmortem examination of the 12 pigs with a double orifice showed the desired central placement of the clip perpendicular to the line of leaflet coaptation. No significant inferior vena cava, right atrial, atrial septal, left atrial, leaflet, left ventricle, or chordal trauma was observed in any animal. This included the studies that required inversion of the clip for repositioning as well as the 2 in which the clip did not retain one leaflet. The clip successfully approximated the middle scallops of the anterior and posterior leaflets and was deployed perpendicular to the line of coaptation, creating a functional double-orifice valve.

**Discussion**

This study demonstrates for the first time the short-term success of a catheter-mediated mitral valve repair in a nondiseased porcine model. This is the first endovascular adaptation of the surgical edge-to-edge mitral valve repair. The clinical success and durability of the surgical edge-to-edge repair is documented.10 Ineffective coaptation of the mitral valve leaflets is the mechanical basis of MR and is only indirectly addressed by most conventional surgical repair techniques. By fastening the leaflets together, the edge-to-edge repair ensures a fixed area of coaptation, allowing the remainder of the line of coaptation to close physiologically without disturbing the subvalvular or annular architecture and function. This preserves, if not improves, left ventricular function, which can be of critical importance for patients with impaired left ventricular function.11 Isolated edge-to-edge repair has also, in an animal model, been shown to preserve exercise-induced annular dilatation.12

Improved postoperative functional status and overall freedom from reoperation for surgical edge-to-edge repair has been reported to be 95% at 6 years.10 This durability is not surprising because the mathematically modeled stresses and net force on the point of mitral valve coaptation are minimal.13 Systolic forces applied to the valve by the left ventricle at the coaptation site are not only parallel to the annulus, but the force on each leaflet is symmetric and opposite the force...
on the opposing leaflet. This favors minimal systolic stress where coaptation occurs.\cite{14} The greatest stress on the leading edge of the leaflets and point of apposition occurs in diastole when the transvalvular gradient is typically only several millimeters of mercury. The surgical edge-to-edge repair in clinical series has not resulted in mitral stenosis.\cite{15}

The simplicity and proven efficacy of edge-to-edge repair make it attractive for an endovascular method of repairing either the structurally or functionally deficient mitral valve. The present study demonstrates that a mitral valve edge-to-edge repair can be successfully performed on the beating heart in an animal model without cardiopulmonary bypass using a catheter-based endovascular system. The clip was successfully deployed with successful approximation of the middle scallops of the anterior and posterior leaflets in the majority (12 of 14; 86%) of study animals. Retrospective analysis of the 2 cases in which the anterior leaflet was not well grasped revealed correctable deficiencies in technique, including improper clip arm opening and improper analysis of echocardiographic images. The porcine model provides a challenging model for demonstrating functionality of the endovascular CVRS for several reasons. The pig mitral valve leaflets are thinner than human leaflets, providing a potentially more rigorous test of the atraumatic features of the devices and procedure. In addition, the porcine interatrial septum is a diminutive structure, and the pig’s left atrium provides limited space to manipulate the catheters, especially in comparison to the dilated left atrium associated with human MR. Through experience, it became evident that to perform a successful grasp in this model, the distal tip of the guide catheter needed to be located \( \approx 2 \) cm above the plane of the annulus. The manipulations required to establish this height included crossing the septum at least 15 mm above the anular plane. It was also learned that to predictably grasp the leaflets, the clip arms should be open to at least 120°, and the center axis of the clip-delivery catheter needed to be positioned relatively perpendicular to the valve plane and in line with the long axis of the ventricle. Significant deviation in an anterior, posterior, medial, or lateral direction produced a suboptimal grasp. This deviation was appreciated with echocardiography and, given the design features of the catheter and the clip that allow for repositioning, easily corrected.

The present study is limited to the short-term evaluation of the endovascular edge-to-edge valve repair system. Long-term animal data are necessary to assess long-term device performance. Extended animal data (up to 12 months) are being analyzed. The clip system has also been evaluated in an animal model of MR for a design conformation and a better appreciation of its applicability and effectiveness. Although extrapolation to human pathology is difficult, it is possible that the clip system could have limited value in subsets of patients with extreme pathology including rheumatic disease, a ruptured papillary muscle, or extreme mitral annular dilatation.

This study introduces the first technology for endovascular edge-to-edge mitral valve repair. The safety and efficacy of the described system in humans experiencing MR remain to be proven; however, the success of placing the clip in a short-term animal model provides encouraging support for a human clinical trial. As a percutaneous intervention in the catheterization laboratory, the technique offers the opportunity for substantial reduction in the morbidity and trauma associated with mitral valve surgery. The technology could also provide a therapeutic alternative for patients with significant MR and advanced left ventricular dysfunction who would not survive the stress of a surgical intervention.

Acknowledgments

This study was supported by a grant from Evalve, Inc.

References

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_Circulation_. 2003;108:1990-1993; originally published online October 6, 2003;
doi: 10.1161/01.CIR.0000096052.78331.CA
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/108/16/1990

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