Percutaneous Treatment of Mitral Regurgitation

Jean-Bernard Masson, MD; John G. Webb, MD

Percutaneous mitral valve therapy became a reality more than 25 years ago with the first description of balloon valvuloplasty for rheumatic mitral stenosis. More recently, percutaneous closure of paravalvular leaks after surgical valve implantation has been shown to have a potential, but limited, role. However, valvular mitral regurgitation (MR) remains largely the purview of surgery. Recently, the potential for less invasively replicating these successful surgical procedures without the need for thoracotomy or cardiopulmonary bypass has generated considerable interest. For the most part, these new approaches are modeled after established surgical strategies.

Percutaneous approaches to mitral repair can be broadly divided into procedures that address the various components of the mitral valve. For purposes of discussion, the mitral valve can be considered to have several component parts: leaflets, subvalvular apparatus (chordate tendinae and papillary muscles), annulus, left atrium, and left ventricle. All are integral to the normal function of the mitral valve and each is a potential avenue for repair. Although many such avenues may not lead to an effective surgical option, it may be unwise to dismiss the possibility that others will achieve some measure of success. We briefly review the current percutaneous therapies being developed and evaluated for the management of MR. The current status of various percutaneous therapies is presented in Table 1.

Leaflet Repair

Complex leaflet repair is currently beyond the reach of a percutaneous approach. However, the relatively simple but, in selected patients, effective “double-orifice” surgical repair initially described by Alfieri and coworkers can be reproduced. In the surgical procedure, the free edges of the mitral leaflets are sutured together in the mid portion creating 2 separated orifices. Generally, surgical leaflet repair is combined with implantation of an annuloplasty ring. The surgical literature suggests that the absence of a ring is associated with suboptimal results and the frequent need for reoperation in patients with more severe MR. This remains the subject of considerable debate.

Two percutaneous leaflet repair procedures have been evaluated to date. The Mobius device (Edwards Lifesciences, Irvine, Calif) used a transeptal suction catheter to grasp the mitral leaflets and deploy percutaneous sutures. Although animal and human trials demonstrated feasibility, the procedure was complex and is not currently being pursued.

The Mitraclip device (Evalve, Inc, Menlo Park, Calif) has proven relatively safe and often effective. Using a multiaxial transeptal catheter system, a metallic clip is used to grasp and approximate the free edges of the 2 leaflets (Figure 1). Transesophageal echocardiographic guidance is used to position the implant and assess the effect. If not satisfactory, the clip can be removed or repositioned or an additional clip can be implanted. Animal histopathologic studies demonstrated encapsulation of the device 3 months after implantation.

The phase I feasibility trial (EVEREST I) included 55 patients with functional or degenerative MR grade ≥3 originating from central malcoaptation. Of the 49 patients in whom a clip was implanted, MR grade was reduced to ≥2+ in 42 (86%). This benefit seemed durable at 6 months.

The ongoing EVEREST registry includes EVEREST I and nonrandomized (roll-in) EVEREST II patients. Clip implantation was successful in 89% of 104 patients with MR grade reduced to <2 in 79 (76%). Success was associated with a sustained clinical benefit (improvement in New York Heart Association class in 73% at 1 year) and a reduction in left ventricular diameter.

Procedural success rose and procedural duration fell as experience increased. Adverse outcomes were infrequent with only 1 in-hospital death and no clip embolization. There was a significant postprocedural increase in transmitial gradient (1.7 ± 0.9 to 4.1 ± 2.2 mm Hg, P < 0.001). Although clinically significant iatrogenic mitral stenosis has not been observed this remains a possibility, particularly with the use of multiple clips. Mitral valve surgery was subsequently performed in 28 patients (26.9%) due to an unsatisfactory reduction in MR. Reassuringly, surgical repair was successful in 20 patients (71.4%). Whether options for surgical repair decline due to leaflet injury late after clip implantation or with a greater number of clips is unknown.

The great majority of patients evaluated had MR as a consequence of abnormal mitral leaflet morphology associated with prolapse. To date, there has been limited experience with functional MR. In an echocardiographic substudy of the EVEREST registry, 8 of the 37 patients had functional MR with normal leaflet morphology. Interestingly, this small cohort derived a benefit similar to that of the overall group.
in terms of MR reduction and favorable left ventricular remodeling.13,18

The pivotal EVEREST II trial randomized almost 300 patients with MR grade ≥3 in a 2:1 fashion to Mitraclip implantation or surgical mitral valve repair or replacement. Strict echocardiographic anatomic criteria and exclusion of patients with severe left ventricular dysfunction or annular dilation mean the trial will assess primarily patients with structural valve disease.18 The primary efficacy end point is freedom from death, surgery for valvular dysfunction, or MR grade ≥3 at 1 year. Enrolment is now complete and results are awaited. Potential concerns with respect to a percutaneous edge-to-edge procedure are many. Although efficacy has been demonstrated in patients with isolated prolapse, efficacy in functional MR is less well established. Midterm durability is established, but long-term durability is not known. Concomitant annular repair is thought by many to be a necessary adjunct to surgical edge-to-edge, and by implication percutaneous, repair. Late implications of leaflet injury for subsequent surgical repair are also a concern. Nevertheless, preliminary safety and efficacy data have been judged sufficient for CE mark clinical release in Europe.

### Coronary Sinus Annuloplasty

Mitra annuloplasty using an undersized ring is a routine component of surgical mitral valve repair.19,20 A number of percutaneous devices have attempted to reproduce the beneficial effects of surgical annuloplasty by taking advantage of the proximity of the coronary sinus to the mitral annulus.21 The coronary sinus and its major tributary, the great cardiac vein, parallel the annulus of the mitral valve along its posterior and lateral aspect (Figure 2). The epicardial coronary venous system is readily accessible from the internal jugular vein as the confluence of the coronary sinus drains directly into the right atrium. Percutaneous approaches have generally used internal jugular or subclavian access to the right atrium to allow intubation of the coronary sinus. Various remodeling devices (Figure 3) can be introduced into the coronary sinus, with the objective being to displace the adjacent posterior mitral annulus toward the anterior aspect of the annulus and thereby improve coaptation of the mitral leaflets.

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### Table 1. Current Status of Percutaneous Mitral Valve Repair Procedures

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<th>Approach</th>
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<th>Current Status</th>
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<tr>
<td></td>
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<td>Edwards Lifesciences</td>
<td>First in man study completed; Not under active investigation</td>
</tr>
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*Use both coronary sinus and atrial anchors to remodel the left atrium and mitral annulus.

![Figure 1. A, Mitraclip device in its open position. B, Evalve delivery system.](http://circinterventions.ahajournals.org/Downloaded from)
increasingly used in patients with heart failure and benefit in MR has been suggested. Only a few patients have had coronary sinus pacing leads placed after coronary sinus annuloplasty.

The MONARC percutaneous transvenous annuloplasty device (Edwards Lifesciences) consists of a stent-like anchor placed in the great cardiac vein, a connecting bridge, and a second anchor located proximally at the coronary sinus ostium. The compressed device can be introduced from the jugular vein using a long sheath. Once positioned within the cardiac venous system, the sheath is withdrawn allowing the self-expanding nitinol alloy anchors to expand, providing fixation (Figure 4). Tensioning the device before deployment of the proximal anchor allows for acute shortening of the coronary sinus. In addition, the nitinol bridge segment is constructed like a spring with biodegradable spacers. Over a few weeks the spacers dissolve and the bridge shortens, the anchors are drawn together and the coronary sinus shortens further. Thus, there is both an acute and delayed effect.

A small feasibility study suggested a reduction in MR. However, the apparent benefit was not sustained, possibly due to separation of the bridge and anchor in some patients. A reinforced version of the device was evaluated in the EVOLUTION I feasibility trial, which enrolled 72 symptomatic patients with grade ≥2 functional MR. Interim analysis found a reduction in MR severity and functional class in the majority of patients (J. Harnek, MD, personal communication). The larger EVOLUTION II trial will soon evaluate the safety and efficacy of the MONARC device in patients with grade 3 or 4 functional MR.


Figure 2. Computed tomography images showing relationship between the plane of the mitral valve (MV), the left circumflex coronary artery (LCx) and the coronary sinus (CS). A, The CS is located to the atrial side of the plane of the MV and often passes over the circumflex artery or its branches. B, Close relationship between the CS and tributary veins with the circumflex artery and obtuse marginal branches.

Figure 3. Coronary sinus annuloplasty devices. A, CARILLON XE. B, MONARC. C, Percutaneous transvenous mitral annuloplasty device. D, Percutaneous mitral repair device.

Figure 4. Schematic representation of a coronary annuloplasty procedure with the MONARC device. A, The delivery catheter is introduced from the jugular vein to the right atrium and coronary sinus. B, Deployment of the distal anchor in the anterior interventricular vein. C, The proximal anchor is deployed at the ostium of the coronary sinus, and the delivery system is removed.
nitinol anchors connected by a wire. The distal coronary sinus anchor is deployed, manual tension is applied to the connecting wire, and then the proximal anchor is deployed. As shortening of the coronary sinus is immediate, the effect on MR and the potential for coronary compression can be readily assessed by echocardiography and angiography. If necessary, the amount of tension can be adjusted or the device can be retrieved before final release.

Initial evaluation demonstrated a reduction in annular dimension and MR severity; however, anchor slippage was a problem. The modified CARILLON XE device was evaluated in the multicenter AMADEUS trial in which permanent device implantation was achieved in 30 of 43 patients. In some cases, the device was removed before final release because of lack of MR reduction or to avoid apparent arterial compression. Quantitative echocardiographic assessment of MR suggested benefit with an acute reduction in MR by a mean of 1 grade.

The Percutaneous transvenous mitral annuloplasty device (Viacor, Inc, Wilmington, Mass) represents a third approach to coronary sinus annuloplasty. A catheter is implanted in the coronary sinus using a subclavian cutdown. Metallic rods are placed within the catheter with the intention of deflecting the coronary sinus and adjacent posterior annulus anteriorly. Surgical re-access to the subcutaneous pocket allows future rod exchange if necessary. Temporary implants suggested efficacy, and the subsequent PTOLEMY trial found a reduction of MR by at least 1 grade was achieved in 13 of 19 patients with limited follow-up suggesting durability.

Atrial Remodeling
The variable relationship of the coronary sinus and great cardiac vein to the mitral annulus is an obvious major limitation of any approach focused solely on this anatomic relationship. The MONARC coronary sinus device does extend its distal anchor into the anterior interventricular vein and consequently may have some effect on the left ventricle itself, albeit probably minor. Other groups have tried to combine an anchor in the coronary sinus with a second anchor in the right atrium in the hopes of more reliably applying force the plane of the mitral annulus.

As with the purely coronary sinus approaches, the Percutaneous Septal Shortening System (PS3, Ample Medical Inc, Foster City, Calif) uses transvenous access to the right atrium to allow placement of an anchor in the coronary sinus adjacent to the mitral P2 scallop (Figure 5A). However, an atrial transeptal puncture allows implantation of the second anchor in the interatrial septum. A magnetic catheter system facilitates placement of a wire connecting these 2 anchors. Tensioning this wire reduces the diameter of the mitral annulus. Ovine studies and temporary human implants have demonstrated a reduction in antero-posterior annulus diameter and MR severity.

More recently reported is a somewhat similar percutaneous mitral annuloplasty procedure in which helical screws are implanted through the wall of the coronary sinus directly into the myocardium adjacent to the mitral P2 scallop (Figure 3D). A second set of screws are implanted in the right atrium near the posteromedial trigone. Tensioning a polyester tether between the 2 sets of anchors similarly remodels the mitral annulus. A small porcine study suggests efficacy and durability.

Direct Annuloplasty
Direct modification of the mitral annulus is the most obvious means of reproducing the effects of surgical annuloplasty. Annuloplasty rings that can be introduced through a catheter are one possible approach; however, reliable methods of positioning and fixation have proved problematic. Direct modification of the mitral annulus using a radiofrequency catheter to heat and shrink annular collagen has been proposed (QuantumCor Inc, Lake Forest, Calif). When the mitral annulus dilates, it is primarily the less fibrous posterior portion of the annulus that is involved. Surgical correction typically involves plication of the posterior annulus in conjunction with implantation of a prosthetic ring. Some surgical experience suggests that suture plication of the posterior portion of the annulus can offer benefit even without a ring. Current percutaneous approaches use a catheter advanced from the
femoral artery into the left ventricle to access the left ventricular attachment of the posterior leaflet.

The Mitralign Percutaneous Annuloplasty System (Mitralign Inc, Tewksbury, Mass) uses a guide catheter passed between the 2 papillary muscles to access this subvalvular space in the region of the mitral P2 scallop (Figure 6). The Accucinch system (Guided Delivery Systems Inc, Santa Clara, Calif) uses a guide catheter to access this same space, but enters medial or lateral to the papillary muscles. In both systems several anchors are implanted in the subannular ventricular myocardium that corresponds to the mitral valve annulus (Figure 7). Linking sutures can be tensioned like a belt shortening the posterior annulus. Human experience been initiated with the Mitralign system and similar trials of the Accucinch system are anticipated shortly.

Ventricular Remodeling

The iCoapsys device (Myocor Inc, Maple Grove, Minn) is designed to produce a reduction in MR by remodeling the left ventricle (Figure 5). This percutaneous device is implanted using a subxiphoid pericardial access sheath. Using a sophisticated positioning system, 2 fixation pads are placed on the surface of the left ventricle, 1 anterior and 1 posterior. Left ventricular puncture allows a cable to connect the 2 pads. Tensioning the cable draws the 2 pads together. As the anteroposterior diameter of the left ventricle is reduced, the anteroposterior dimension of the mitral annulus also reduces, hopefully resulting in improved leaflet coaptation, reduced chordal tethering, and improved left ventricular function.

There is considerable prior experience with an earlier, surgically implanted version of this device (Coapsys). The TRACE feasibility and the randomized RESTOR-MV trials in patients with ischemic, functional MR undergoing bypass surgery demonstrated a reduction in MR and left ventricular volume as well as symptomatic benefit comparable with mitral surgery. Feasibility of the percutaneous iCoapsys procedure has been demonstrated in an ovine model, and recently initial human implants have been performed.

Other Novel Approaches

Surgical mitral valve repair often incorporates chordal repair, implantation, or removal. Transcatheter and percutaneous chordal procedures are currently under development, including chordal cutting and chordal implantation.

Valve Replacement

Although surgical repair of the mitral valve is relatively mature, percutaneous repair is unlikely to offer the same degree of efficacy in the near future. In the absence of an effective transcatheter repair, transcatheter valve implantation might offer a very desirable alternative. Transcatheter implantation of a valve stent within a degenerated surgical mitral bioprosthesis has been accomplished, at least to some degree demonstrating the feasibility of this approach. However, implantation of a valve stent within a native mitral valve is problematic due to the saddle shape of the native annulus, chordal structures, limited fluoroscopic landmarks, and the need to avoid obstruction to the left ventricular outflow tract. Nevertheless, a number of groups have pursued this goal, generally combining a self-expanding valved stent (Figure 8) with percutaneous transseptal, direct left atrial, or transapical access to the mitral valve. Clinical trials are anticipated.

Summary

Percutaneous approaches to MR remain largely investigational. Available evidence is most supportive of a clinical role for percutaneous edge-to-edge repair, the only procedure currently in clinical use. Whether this will offer an effective and durable option only for a small number of patients with prolapse or for a much broader population of patients with functional MR is not yet known.

Preliminary evaluation of early percutaneous annuloplasty procedures suggest the potential for limited efficacy in selected patients. Whether these procedures will result in meaningful benefit is unknown. Increasingly, complex percutaneous repair procedures are being developed and seem promising. At the same time, the difficulties faced in accomplishing complex mitral repair by percutaneous means may
result in increasing interest in transcatheter mitral valve implantation. Whether transcatheter management of MR will assume a major therapeutic role remains uncertain.

Disclosures
Dr Webb is a consultant for Embrella Inc and Boston Scientific Inc, and has been a consultant to Edwards Lifesciences Inc, Guided Delivery Systems Inc, Mitralign Inc, Kardium Inc, and St Jude Medical Inc.

References


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