Percutaneous Mitral Valve Repair
A Fertile Field of Innovative Treatment Strategies

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The mitral valve is a complex structure composed of the leaflets, annulus, chordae tendineae, and papillary muscles. Competency of the mitral valve is dependent on the proper function of each of these component structures. The pathophysiological triad of mitral regurgitation (MR) was originally described by Carpentier in 1983. It included the etiology of the valve lesion, the valve lesion itself, and the resultant valve dysfunction. He subsequently described a classification of leaflet dysfunction in MR that is commonly used and relevant for patient selection and evaluation of percutaneous mitral valve repair (PMVR). In type I dysfunction, there is normal leaflet motion, and valvular incompetence is due to either annular dilatation or leaflet perforation. Type II mitral dysfunction includes patients with increased leaflet motion (prolapse) of one or both leaflets so that there is failure of coaptation during systole resulting in mitral regurgitation. Patients in this category are those with degenerative myxomatous disease of the valve with chordal and/or papillary muscle elongation or rupture. Patients with type IIIa dysfunction have restriction of leaflet motion during both systole and diastole caused by leaflet and subvalvular apparatus thickening and fusion (rheumatic heart disease). The cause of valvular incompetence in patients with type IIIb dysfunction is restricted leaflet motion during systole caused by apical displacement of the papillary muscle from ventricular enlargement in dilated cardiomyopathy (functional MR) and lateral displacement of a posterior papillary muscle in ischemic MR. Patients may have a combination of causes of dysfunction (annular dilation, apical papillary muscle displacement), especially in advanced disease. Patients with MR for purposes of surgical and percutaneous intervention can broadly be categorized as having intrinsic disease (type II) and functional or ischemic (type I or type IIIb).

We are now embarking on a new era in the treatment of valvular heart disease with the introduction of percutaneous and minimally invasive devices and techniques to address valvular dysfunction without conventional surgical repair/replacement. Pathology of all 4 cardiac valves has now been treated in early stage clinical feasibility (pilot) trials. There are at least 30 percutaneous valve programs currently being developed by 24 different companies. Two of the percutaneous aortic valve devices and 5 of the mitral valve devices are in various stages of clinical trials, ranging from feasibility to pivotal at the present time.

For patients with MR caused by mitral valve prolapse (type II), 2 percutaneous devices have been introduced, the Mitra-Clip (Evalve, Inc, Redwood City, Calif) and the Mobius II (Edwards Lifesciences, Irvine, Calif) Both devices are based on the edge-to-edge technique described by Alfieri et al. This technique creates a double orifice valve by attaching the free edges of the leaflets together correcting the increased leaflet motion and, therefore, the regurgitation. Alfieri et al have used this surgical technique as an adjunct to other valve repair techniques, as an alternative to complex repair in bileaflet prolapse, or with heavy annular calcification. Of note is the fact that a concomitant annuloplasty was also performed in 80% of the patients. Midterm follow-up of patients without an annuloplasty confirmed suboptimal results. Results of the Evolve pilot trial, EVEREST I (Endovascular Valve Edge-to-Edge REpair STudy), have recently been published. Of 27 patients entered into the trial, 14 (52%) had the mitral clip device in place with 2+ or less mitral regurgitation at 6-month follow-up. Nine patients (33%) had undergone surgical correction. This device is now in a multicenter pivotal trial (EVEREST II) with 2:1 randomization against conventional mitral valve repair in 30 centers in the United States. The surgical standard for correction of mitral valve prolapse has recently been published. In a single-center series of 702 patients, 12-year freedom from reoperation was 94.1%, with 12-year freedom from moderate or severe mitral regurgitation at 73.3%. As addressed below, the conundrum is how to evaluate first generation percutaneous technology against mature surgical procedures while ensuring patient safety and interest and yet allowing new technology to be introduced into clinical medicine.

A myriad of surgical devices have been introduced with the purpose of treating functional MR. Correction of functional MR is based on the principle of correcting leaflet malcoaptation by decreasing size of the mitral annulus. Elegant studies by Miller (Tibayan et al) in the animal model and Jatene (Huebet al) in autopsy studies have demonstrated that there is a dilation of all of the annulus in chronic functional MR caused by either ischemic or idiopathic dilated cardiomyopathy. The degree of ventricular dilation does not correlate with the degree of annular dilation or MR, but the most significant change is an increase in the septal-lateral or anterior-posterior diameter. This forms the basis for surgical correction of functional MR by use of an undersized complete annuloplasty ring firmly anchored in the fibrous trigones.
Although the procedure can be performed with acceptable morbidity, the permanence of the repair, the effect on ventricular remodeling, and impact on clinical outcomes remain unclear. This same principle of remodeling the mitral annulus by decreasing the septal-lateral diameter is the basis for a variety of innovative percutaneous and minimally invasive surgical devices. Most commonly, these devices are placed in apposition to the mitral annulus via the coronary sinus to perform a posterior annuloplasty. Proof of concept has been demonstrated in the animal model and now in early clinical feasibility studies. The efficacy of this approach, however, faces multiple challenges, including the inconstancy of the relation between the coronary sinus and the posterior mitral annulus, the inability to reliably anchor the devices in both fibrous trigones, possible impingement of the device on the circumflex coronary artery, and annular calcification. In some patients, tethering of the leaflets by traction from the apically displaced papillary muscles rather than annular dilation is the primary pathophysiological mechanism of MR, and the efficacy of the coronary sinus devices is not clear with this pathology. Another innovative technique to correct functional MR is a catheter-based approach, which uses radiofrequency to shrink the posterior mitral annulus.

The other technique of annular remodeling uses a “bridge and tether” apparatus to decrease the septal-lateral diameter. This technique is referred to “SLAC” or septal-lateral annular cinching. By decreasing the septal-lateral diameter by cinching rather than by annuloplasty, dynamic annular and leaflet function may be preserved. A surgical technique to perform this cinching has been demonstrated clinically with the Myocor Coapsys device (Myocor, Inc, Maple Grove, Minn). This device includes an anterior and posterior epicardial pad connected by a transventricular chord that can be drawn, thereby cinching the annulus in a septal-lateral dimension. Proof of concept has now been demonstrated in 30 patients. Taking this same concept to a percutaneous approach of treating functional mitral regurgitation is the report in this issue of Circulation by Rogers et al. Using the concept of SLAC, the PS3 system (percutaneous septal sinus cinching) percutaneously places a bridge and strut system on the atrial rather than the ventricular side of the mitral annulus. One end of the bridge is anchored in the coronary sinus after magnetically mating with the transatrially delivered strut, with the other end anchored to an Amplatzer PFO Occluder (AGA Medical Corporation, Golden Valley, Minn) in the atrial septum. A number of the shortcomings of the coronary sinus annuloplasty devices, including anatomic relations, anchoring, circumflex coronary artery impingement, and calcification, are potentially obviated by this device. Because of the angle of placement, there is not true septal-lateral thinning; however, this may actually prove to be advantageous in ischemic MR where there is eccentric regurgitation due to asymmetric dilation of the posteromedial portion of the annulus from the posterior papillary muscle traction.

Numerous issues exist in the developmental, regulatory, and clinical aspects of these devices. First are the demonstration of efficacy and the design of clinical trials. A joint position statement from 2 cardiac surgical and 1 cardiology society with input from the Food and Drug Administration and Center for Medicare and Medicaid Services offers input regarding these issues. Pivotal trials for regulatory approval of any new percutaneous valve device will be required to be randomized against current treatment of the population studied. Particularly difficult will be the task of fairly comparing first generation technology against mature standards of care while ensuring patient safety. Factored into this will be the question as to what is an acceptable decrement in efficacy that is adequate as a trade-off for an increase in safety or less invasiveness. For example, how does one compare a procedure that results in a decrease in MR from 4+ to 2+ (severe to mild) and back to normal activities in a week to a procedure that decreases MR from 4+ to 0 with a return to baseline in a month? Careful clinical trial design is critical, with both safety and efficacy end points compared with either surgery in surgical candidates or optimal medical therapy in nonsurgical candidates. With functional MR, the use of end points other than mortality including improvement in congestive heart failure stage, need for repeat hospitalization, ventricular remodeling, and change in ejection fraction will be necessary to demonstrate value.

As with most early-stage, less invasive procedures in medicine, clinical reality will not match expectations as quickly as innovators, investigators, clinicians, and patients wish. However, by device iteration, procedure development, and careful, well-designed clinical trials with investigator equipoise and patient interest paramount, a whole new paradigm of treatment can be safely and expeditiously developed. As it is true with many other less invasive procedures in medicine including laparoscopic cholecystectomy, arthroscopy, and percutaneous coronary intervention, the population able to benefit from these interventions will ultimately be significantly expanded.

Disclosures
None.

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