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Percutaneous Valve Therapies

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Executive Summary

Many would say that the last frontier in interventional cardiology is percutaneous valve repair and replacement. The first percutaneous aortic valve replacement was performed in 2002 using an antegrade approach in a patient with critical aortic stenosis. The antegrade approach allowed for a large venous access site, but was limited by device maneuverability, mitral valve compromise during guidewire manipulation, and inadequate visualization of the native aortic valve. The first retrograde placement was performed in 2005. This approach was technically more demanding due to native valve calcification and the need for large bore arterial access, but overcame many previous limitations. The next generation devices are focused on increased flexibility, miniaturization of access catheters, and repositionable valves. Attempts at percutaneous mitral valve repair are as varied as the pathophysiologic mechanisms of mitral regurgitation. Most of these techniques are modifications of surgical therapies, such as edge-to-edge mitral leaflet repair and annuloplasty. Other approaches involve remodeling of the left ventricular chamber in conjunction with the mitral valve. Recognition of different mechanisms of mitral regurgitation in different patient groups is vital for successful percutaneous treatment. While problems with anatomic variability and device malfunction have been encountered, progress is being made. Large scale trials comparing percutaneous valve replacement and repair with surgery have just begun, but prospects for the future of these therapies are good.

Introduction

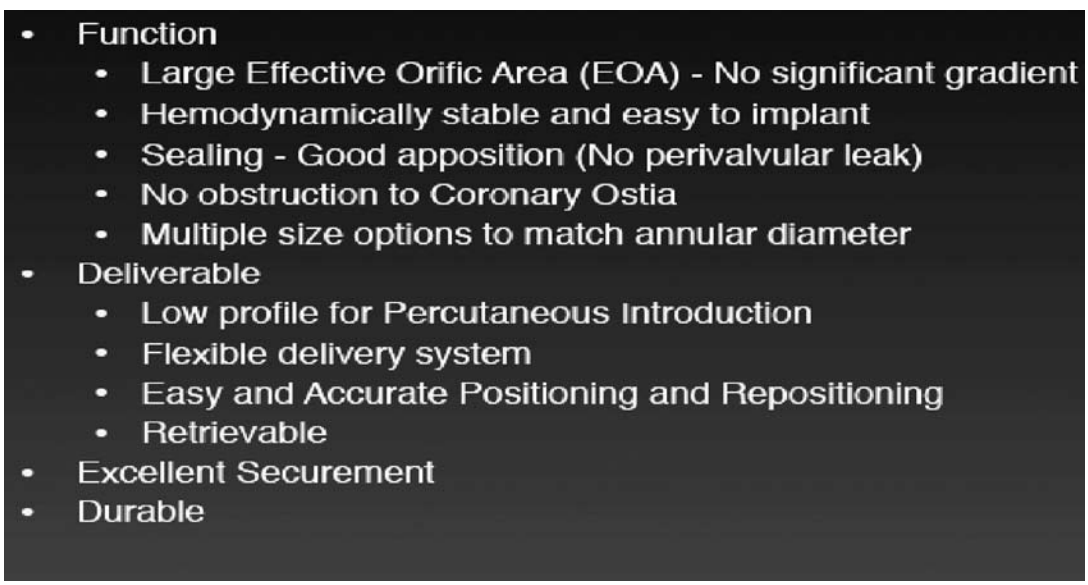
The prevalence of valvular disease increases with age, reaching up to 13.3% in those 75 years or older [1]. Open surgical aortic valve replacement (AVR) in symptomatic patients with aortic stenosis (AS) is the gold-standard and results in excellent symptom relief and long-term survival in most patients. However, a growing number of patients are poor surgical candidates due to advanced age and multiple comorbidities that impose an increased risk of complications both during and after surgery [2]. Consequently, as much as 30% of critically ill patients with valvular heart disease are refused surgical intervention, even in the setting of isolated AS [3,4]. Additionally, 200,000 patients per year are diagnosed with mitral regurgitation, 50,000 of whom require surgical treatment. The desire for less invasive therapies in this often high-risk and minimal option group has inspired the development of techniques for percutaneous aortic valve replacement and non-surgical mitral valve repair. During the past 2 decades, major advances have occurred in the development of catheter-based interventions that may permit more of these high-risk patients to benefit from percutaneous AVR and mitral valve repair. An overview of current devices and techniques, including an update of the past year's experiences, will be presented.

Aortic Valve Replacement

Antegrade Approach

The first successful percutaneous AVR took place in 1992 in a swine model by Andersen and colleagues [5]. Eight years later, Bonhoeffer and his group reported the first human use of a stent-mounted bioprosthesis for pulmonary valve replacement [6]. Subsequently in 2002, Alain Cribier and colleagues implanted the first percutaneous heart valve (PHV, Percutaneous Valve Technologies, Fort Lee, NJ) in the aortic position of a patient with critical AS who was not a candidate for aortic valve surgery because of multiple comorbidities [7]. The PHV was made of bovine pericardial leaflets sewn into a radiopaque, stainless steel, balloon-expandable stent, 14mm in length and 21-23mm in diameter. It was placed by an antegrade transeptal approach through a 24F sheath in the femoral vein, and resulted in significant hemodynamic improvement. Obstacles to overcome included miniaturizing the profile while maintaining an adequate size valve with a suitable effective orifice area, as well as providing easy deliverability, accurate positioning and optimal securement. These and other desirable features of percutaneous aortic valves are listed in Table 1.

Following this successful placement, Cribier and colleagues reported on 36 high-risk, inoperable patients (mean age 80 years) with severe calcific AS who underwent attempted placement of the PHV as part of the I-REVIVE (Initial Registry of Endovascular Implantation of Valves in Europe) and the RECAST (Registry of Endovascular Critical Aortic Stenosis Treatment) trials [8]. Twenty-seven of these placements were successful (23 antegrade and 4 retrograde). Following the procedure, the aortic valve area improved from an average of 0.6cm^2 to 1.7 cm^2 ($p<0.0001$) and the mean transvalvular gradient decreased from 37mmHg to 9mmHg ($p<0.0001$). Limited visualization of the native aortic



valve and annulus during implantation, perivalvular regurgitation, and anterior mitral valve leaflet injury by the guidewire were all noted problems. However, there were no cases of PHV dysfunction, secondary valve migration, or coronary occlusion. Eleven patients were still alive at 9 to 26 month follow-up, almost all in New York Heart Association class I or II heart failure. The patients in the RECAST trial received the second generation PHV (Cribier-Edwards Aortic Valve, Edwards Lifesciences, Irvine, CA) made of equine pericardium inserted within a reinforced stent (Figure 1a). In addition, their procedures were performed using only an antegrade approach which allowed for easier crossing of the heavily calcified native aortic valve, avoided large bore arterial access, and had a higher success rate (85% vs. 57% with the retrograde technique), but was technically more demanding. The 30-day mortality of 22% in this first-in-man cohort not only reflects the critically ill, high-risk population participating, but also exposes the learning curve associated with this new technology. Given the technical complexity of this approach and the associated risks, the antegrade approach to percutaneous AVR did not gain widespread acceptance.

Retrograde Approach

Retrograde prosthetic aortic valve implantation via the femoral artery has potential advantages and was first reported in 2005 by Hanzel and colleagues [(9)]. The retrograde approach was attempted after the investigators encountered difficulties with the initial antegrade approach. The iliac artery was accessed surgically and a 24F sheath was placed. Rapid right ventricular pacing (200 beats per minute) was performed to "freeze" the heart and facilitate securing and accurately implanting the valve.

Around the same time, Grube and colleagues [(10)] placed the first self-expandable aortic valve prosthesis (CoreValve, Inc., Irvine, CA) (Figure 1b) using a retrograde approach and partial femoral-femoral cardiopulmonary bypass. This commercialized bovine pericardial valve is mounted and sutured in a self-expanding nitinol stent, which has three discrete segments. The lower conical part (annulus level) is covered by pericardium and firmly anchors the prosthesis to the aortic annulus by creating a high radial force to avoid recoil; the middle part (commissural level) carries the valve and is constrained to avoid the coronary ostia; and the upper part (aortic level) expands for fixation in the ascending aorta. Like the PHV, this valve cannot be retracted or moved once it is deployed. This first generation device was used to treat 14 patients with a clinical success rate of 40%, but an in-hospital mortality rate of 45%. The second-generation device was modified and miniaturized (21F). Sixty-three patients were implanted with this second-generation CoreValve resulting in a 91% procedural success rate and 12.7% in-hospital mortality rate [(11)]. The 9% technical failure rate was due to an inability to cross the iliac artery, the native aortic valve, or misplacement of the prosthetic valve. The aortic valve area and mean pressure gradient across the valves significantly improved and 82% of patients had only grade ≤ I paravalvular leak. The recently introduced third generation valve is a tri-leaflet porcine pericardial tissue valve that is inserted through an 18F introducer sheath and has a disposable loading system (CoreValve Revalving™ System, Generation 3). Phase III clinical trials are underway at up to 12 centers in Europe and Canada.

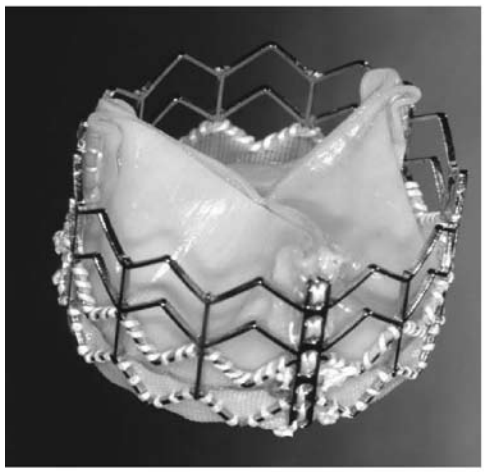
In early 2006, Webb and colleagues presented the results of 18 patients with successful placement of 14 Cribier-Edwards percutaneous valves using the retrograde approach [(12)]. The investigators noted that diligent screening to assure adequate femoral and iliac artery size and patency was needed in order to minimize vascular access issues. In addition, the use of rapid pacing, a deflectable delivery sheath, an option for a larger Cribier-Edwards (26mm vs. 23mm) valve, and other procedural and technical improvements shortened procedure times, facilitated procedural success, and decreased both complications and early mortality. At 2 months post-placement, the all-cause mortality remained low at 11.1%. Two trials are ongoing using the 23mm and 26mm Cribier-Edwards valve via the retrograde approach (the European REVIVE and the US REVIVAL II). Preliminary results of the REVIVAL II (PeRcutaenous EndoVascular Implantation of VALves) trial in high-risk patients with critical AS were presented at the 2006 Transcatheter Cardiovascular Therapeutics conference [(13)]. Fifty-four patients (mean age 82 years) with high- risk comorbidities and critical AS were enrolled. Implant success rate was 87% with 62% of these patients receiving a 26mm valve. In-hospital mortality was 7.4% with 9% neurologic events and 13% vascular complications. There were no late cardiac deaths.

The future of aortic valve replacement is promising with many new devices in development (Table 2). The

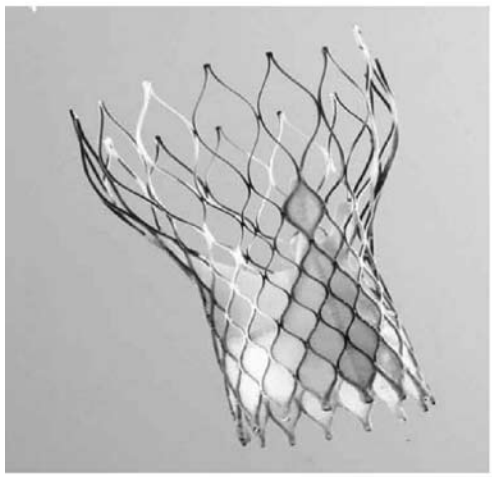
Table 2 **Future Aortic Valve Devices**

Company	Device
Advance Bioprosthetic Surface	Nitinol Cardiac Valve
AorTech International	Elast-Eon Valve
AorTx	Expandable Anchors Aortic Valve
Direct Flow Medical	Serial Annular Inflation Aortic Valve
Endoluminal Technology Research	Unique Geometrical Design
University of Kiel	Lutter Valve
Sadra Medical	Lotus Repositionable Aortic Valve
Jena CardioTech	Aortic Valve Project
The Sorin Group	Percutaneous Valve Project
Heart Leaflet Technology	Aortic Valve Project

Figure 1 **Percutaneous Aortic Valves**

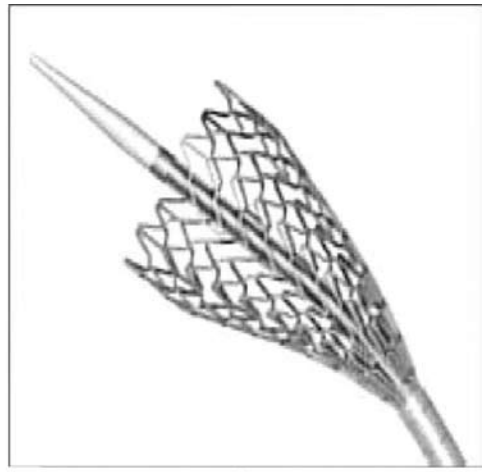


a. Cribier-Edwards Aortic Valve

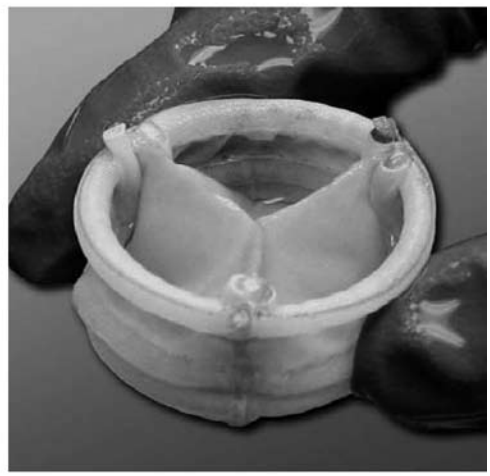


b. CoreValve Aortic Valve

c. AorTx Aortic Valve



d. Sadra Medical Aortic Valve



e. Direct Flow Aortic Valve

AortTx (Palo Alto, CA) valve has a triple hinged supporting ring with rotational crimping to 18F and available in sizes 19–27mm (Figure 1c). Preliminary results of initial clinical experience are encouraging. Implantation of the AorTx valve in eight patients (age 23-76 years) with severe AS was successful without any valve migration and resulted in excellent hemodynamics and minimal or no paravalvular leak (14). Sadra Medical, Inc. (Campbell, CA) has developed a self-expanding, retrievable and repositionable valve (Figure 1d). The Direct Flow valve (Direct Flow Medical Inc, Santa Rosa, CA) is another novel stentless tissue valve with equine leaflets in an inflatable cuff support structure delivered via the retrograde approach (Figure 1e). Once proper positioning is confirmed, the inflation contrast material is replaced with a polymer that hardens in a short period of time creating a valve similar to a surgical bioprosthesis. The safety and feasibility of this valve prosthesis was evaluated in a first-in-man study (not yet published). Six patients were enrolled, 4 had percutaneous placement of the valve and 2 underwent open surgical implantation. Five out of 6 patients had successful implantation with trace paravalvular leak or aortic insufficiency and no mortality. The design of these next generation valves focuses on deliverability, with a smaller profile for insertion, as well as being retrievable and repositionable.

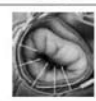
Transapical Approach

John Webb and colleagues reported a technique of prosthetic aortic valve implantation by direct left ventricular access using a beating-heart, catheter-based approach in humans [15]. A left anterolateral intercostal incision was made to expose the left ventricular (LV) apex and by direct needle puncture of the apex, a sheath was introduced in the LV. A Cribier-Edwards valve was advanced over a wire and deployed within the annulus. Valve implantation was successful in all 7 patients with no intraprocedural complications or deaths. Echocardiographic median aortic valve area increased from 0.7 ± 0.1 cm^2 to 1.8 ± 0.8 cm^2. At 6-month follow-up, the aortic valve area was 1.5 ± 0.5 cm^2 with no valve-related complications [16]. This initial experience suggests that the transapical approach may be a potential alternative for patients that are not surgical candidates.

Mitral Valve Repair

The mitral valve is a complex apparatus and the pathophysiologic mechanisms of mitral regurgitation (MR) are varied. These mechanisms were first categorized by Carpentier and colleagues in 1976 [17]. His three tier classification system (Types I, II, and III) qualitates annular size, leaflet mobility and coaptation, as well as papillary muscle function, in determining the structural changes causing mitral regurgitation. Surgical repair attempts to address these structural changes and frequently combines approaches of leaflet revision with annuloplasty and occasionally edge-to-edge repair (Alfieri stitch). These surgical techniques have served as the foundation by which multiple percutaneous approaches have been fashioned. They can be broadly categorized into leaflet (edge-to-edge) repair for patients with adequate leaflet proximity, coronary sinus annuloplasty for the treatment of functional and ischemic MR, direct annular plication mimicking surgical annuloplasty, and shortening of the anterior-posterior dimension of the mitral valve annulus or the left ventricle (Table 3).

Table 3 **Techniques for Mitral Valve Repair**

Technology	Approach	Status
Edge-to-Edge • E Valve • Edwards	**Double Orifice** 	**Clinical**
Coronary Sinus • Edwards • Viacor • Cardiac Dimensions • Viking	**CS Reshaping** 	**Clinical**
Annulus Plication • Mitralign • Guided Delivery Systems	**Posterior Reshaping** 	**Pre-Clinical**
LV Dimension Change • Myocor • Mitralign	**External LA/LV** 	**Clinical/ Pre-Clinical**
Septal-Lateral Shortening • Ample Medical, Inc.	**Internal S-L Shortening** 	**Pre-Clinical**

Mitral Leaflet (Edge-to-Edge) Repair

The first novel surgical approach to mitral valve repair was pioneered by Alfieri [18]. By placing a suture at the edges of the anterior and posterior mitral leaflets, he was able to dramatically reduce the severity of MR. A percutaneous approach to achieve a similar Alfieri-like result utilizes a subvalvular mitral leaflet clip, MitraClip™ (Evalve, Inc., Menlo Park, CA). The clip is placed via an antegrade transseptal approach and creates a double orifice mitral valve (Figure 2a). Transesophageal echocardiography (TEE) is used to assist in the positioning of the clip and evaluation of results. Feldman and colleagues reported the EVEREST I (Endovascular Valve Edge-to-edge REpair STudy) trial, which was a phase I clinical trial of the Evalve system in patients with grade 3 (moderate to severe) or grade 4 (severe) type II MR (19). Of the 27 patients who underwent attempted percutaneous valve repair, 89% had successful clip placement and 64% had less than 2+ MR after one month. Ninety-three percent of these patients continued to have <2+ MR at 6-month follow-up. Furthermore, echocardiographic and hemodynamic measurements after MitraClip repair showed an expected decrease in mitral valve area with no evidence of clinically significant mitral stenosis either immediately after clip deployment or after 12 months of follow up (20). The EVEREST registry has enrolled over 104 patients thus far with clips implanted in 89% of patients, effectively reducing MR to $\leq$ 2+ in 85% of cases, maintained at 24 months. There were no major adverse cardiac events at 30 days and early symptomatic improvement was seen in approximately 70% of patients. An ongoing 2:1 randomized controlled trial, EVEREST II, is currently enrolling patients to percutaneous versus surgical repair. This trial will be pivotal not only in the development of the percutaneous therapy but also in defining the contemporary results of mitral valve surgery since there has never been a prospective trial of mitral valve repair reported in the surgical literature.

Another mitral leaflet repair device, Mobius II™ (Edwards Lifesciences, Irvine, CA), which is currently beginning human trials, also creates a double mitral valve orifice, but through a percutaneously placed stitch joining the middle of the anterior and posterior mitral valve leaflets (Figure 2b). The leaflets are grasped using a suction device and the suture is placed using TEE guidance. While these devices attempt to mimic a surgical approach, the best results often combine the Alfieri stitch with annuloplasty since a substantial number of patients with MR also have evidence of annular dilatation leading to poor leaflet coaptation [21]. Similarly, a percutaneous approach has the potential to combine the edge-to-edge repair with an annular reshaping technique, thus optimizing the reduction of MR.

Coronary Sinus Annuloplasty

Realizing that the coronary sinus (CS) parallels the mitral annulus has led to several percutaneous approaches for mitral regurgitation. Multiple companies are currently testing CS annuloplasty devices. These reinforcement devices are placed within the great cardiac vein (GCV) and the CS, thereby shortening the anterior-posterior (septal-lateral) dimension and decreasing MR. Cardiac Dimensions®, Inc. (Carillon device, Kirkland, WA) and Viacor, Inc. (Wilmington, MA) have both reported their experiences with successful device placement within the CS in ovine models of ischemic MR [22, 23]. The Carillon device (Figure 2c) is placed via the jugular vein into the CS. As it is released, tension is placed on the mitral annulus resulting in a significant reduction of MR, mean pulmonary capillary wedge pressure, and improvement in cardiac output. The Viacor, Inc. annuloplasty device (Figure 2d) significantly reduced the MR jet, the mitral annular anterior-posterior dimension, and the mitral valve tenting area. Follow-up at 50 days remained encouraging, and there was no evidence of coronary sinus thrombosis or occlusion. Human studies with these devices are underway.

Webb and his group recently published the first human experience with the Viking device (Edwards Lifesciences, Irvine, CA) [24]. This CS annuloplasty device has a distal self-expanding anchor, a middle spring-like "bridge", and a proximal self-expanding anchor (Figure 2e). The distal anchor is placed in the GCV and the proximal anchor in the CS. The bridge has shape memory properties that result in shortening forces at body temperature. The anchors draw the CS and the GCV together while the bridge element tenses and straightens, indirectly displacing the posterior annulus anteriorly and reducing the mitral annulus diameter and the anterior-posterior distance. This small pilot study showed some improvement in chronic MR, but 1 out of the 5 patients could not have the device successfully implanted, and 3 of the 4 who did, had evidence of bridge separation or fracture during follow-up. A second-generation device correcting these problems has been created and is currently being tested.

While these devices are based on sound concepts, some early problems need to be addressed. First, the coronary sinus is not always perfectly aligned with the mitral annulus, at times residing atrially along its course. This will temper the overall improvement in MR. Second, the coronary sinus is thin and may be prone to perforation from device manipulation as was seen in one patient presented by Webb et al. Third, the left circumflex coronary artery frequently crosses the coronary sinus at or near the level of the left fibrous trigone. Compression of the circumflex coronary artery is a theoretical consideration and needs to be followed.

Finally, these devices can be bulky and with competition for the coronary sinus by electrophysiologists becoming prevalent, they may pose future obstacles to interventional therapy.

Direct Annular Plication

Some of the challenges posed by the coronary sinus may be eliminated by accessing the left ventricle directly and placing a device on the ventricular side of the mitral annulus. These devices attempt to mimic a true surgical annuloplasty by placing multiple interrelated anchors within the posterior mitral annulus and then using these anchors to change the geometry of the mitral apparatus, hence reducing MR (Figure 2f). Direct annular plication devices are currently being developed by multiple companies and animal models have been encouraging, with the first-in-man experience being planned.

Shortening the Septal-to-Lateral Dimension of the Mitral Valve Annulus

Pathophysiologic studies have demonstrated that septal-to-lateral (SL, same as anterior-posterior) enlargement is the final common pathway in the development of functional and ischemic MR, and that shortening this dimension is critical in alleviating it (25). A study by Rogers and colleagues demonstrated a novel way to ameliorate functional and possibly ischemic MR by directly shortening the SL diameter of the mitral annulus using a tightening bridge (26). The percutaneous septal sinus shortening (PS) system (Ample Medical, Inc., Foster City, CA) uses a series of magnetic catheters in order to create a physical connection between the GCV behind the posterior mitral leaflet and the interatrial septum (Figure 2g). A T-bar anchoring device is placed within the CS/GCV and an attached suture (bridge element) is pulled through the left atrium and connected to a 35-mm Amplatzer PFO occluder (Golden Valley, MN) already placed in the interatrial septum. Once this connection is made between the GCV and the interatrial septum, tension can be applied to the bridge element, effectively shortening the SL dimension. Using an ovine model, the investigators found that following device implantation the SL diameter decreased by an average of 24% ($p<0.001$) and MR was reduced to only trace amounts compared with baseline ($p<0.001$). At 30 days follow-up, the positive results were still present. This device has shown early promise and a temporary device was recently implanted in a first-in-man study, confirming efficacy in significantly reducing MR.

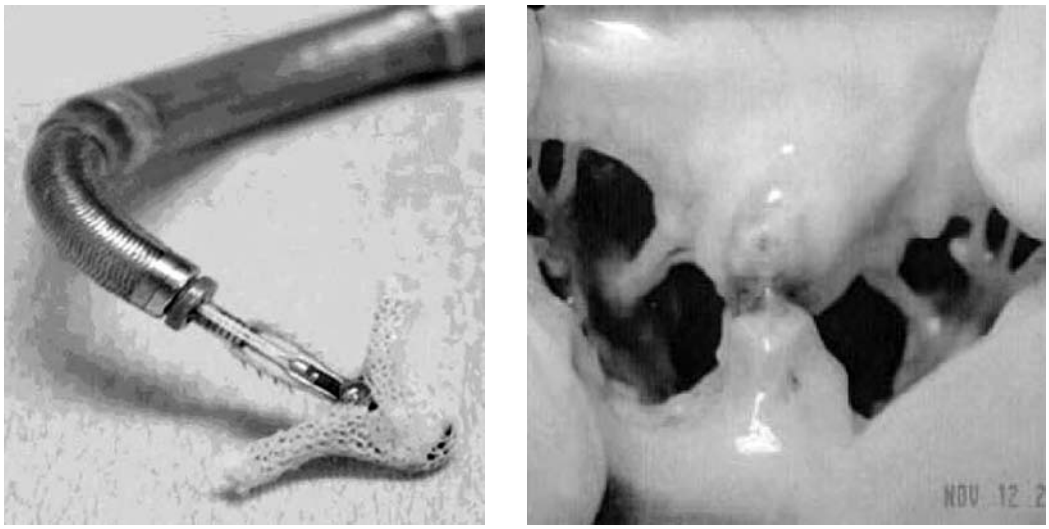
Shortening the Septal-to-Lateral Dimension of the Left Ventricle

The Coapsys device (Myocor®, Inc., Maple Grove, MN) was designed to treat mitral regurgitation due to mitral annular dilatation and papillary muscle displacement. Anchoring devices are placed on the outer left ventricular surfaces in a septal-to-lateral configuration and are connected by a tethering or anchoring suture that passes horizontally through the left ventricle (Figure 2h). A decrease in MR is produced by as the tether is shortened, which is monitored echocardiographically. The initial data from this surgical experience has shown that the Coapsys annuloplasty system is safe and effective at significantly reducing MR, with benefits sustained at one year [27]. A clinical trial (RESTOR-MV) is currently ongoing, randomizing patients undergoing coronary bypass surgery (who also need mitral valve repair for MR) to the Coapsys device or traditional mitral repair.

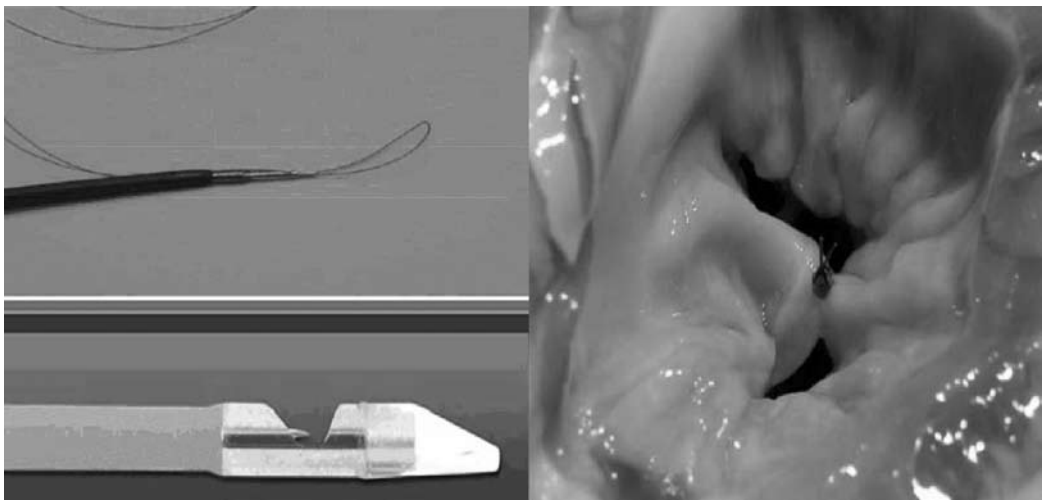
Conclusion

It is clear that a spectrum of devices and techniques are being developed to treat aortic and mitral valve diseases. Some of these approaches will ultimately become successful but will not result in treating all patients with MR or AS. In the near future we will see the advent of large clinical trials randomizing different patient subgroups, not just critically ill ones, to either surgical or percutaneous aortic valve replacement and mitral valve repair. These trials will be burdened by trying to show equivalence between new techniques and well-established surgical approaches. Patience, collaboration, and vision will be needed to allow the promise of these percutaneous methods to be fully realized.

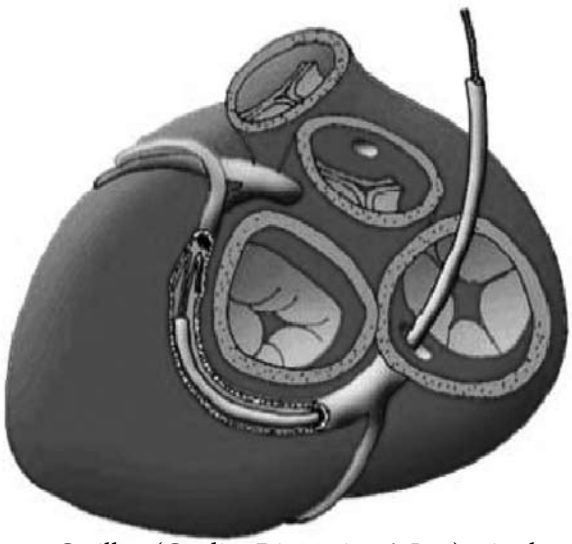
Figure 2 **Mitral Valve Repair Devices**



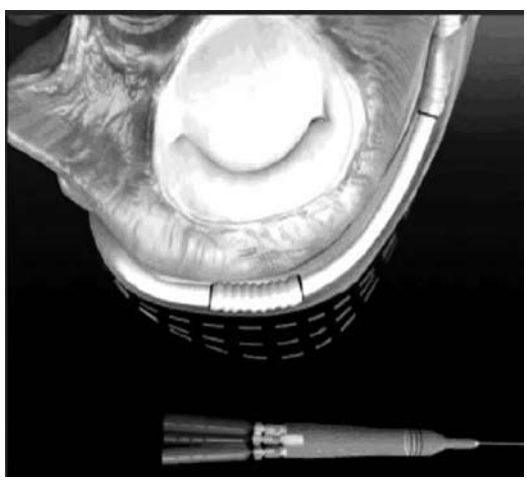
a. MitraClip™ device



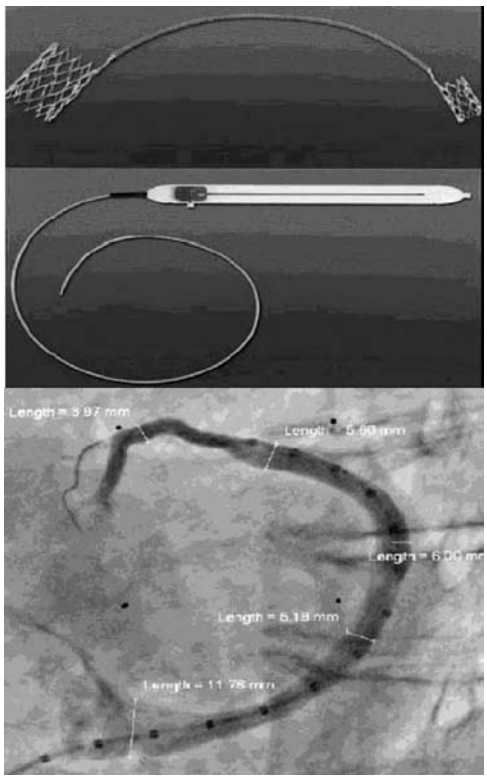
b. Mobius II™ device



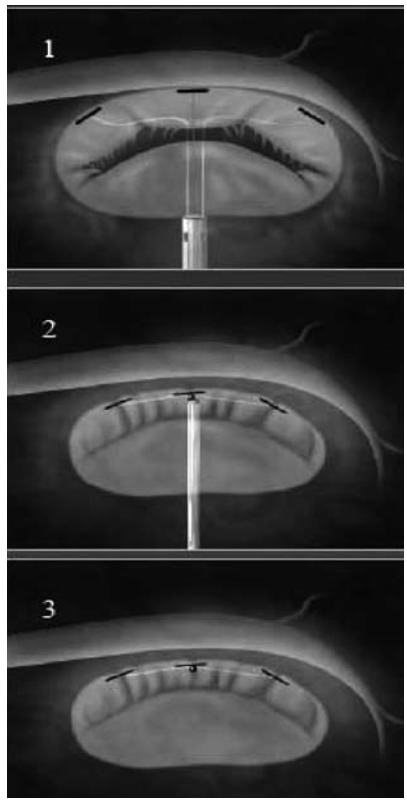
c. Carillon (Cardiac Dimensions®, Inc.) mitral



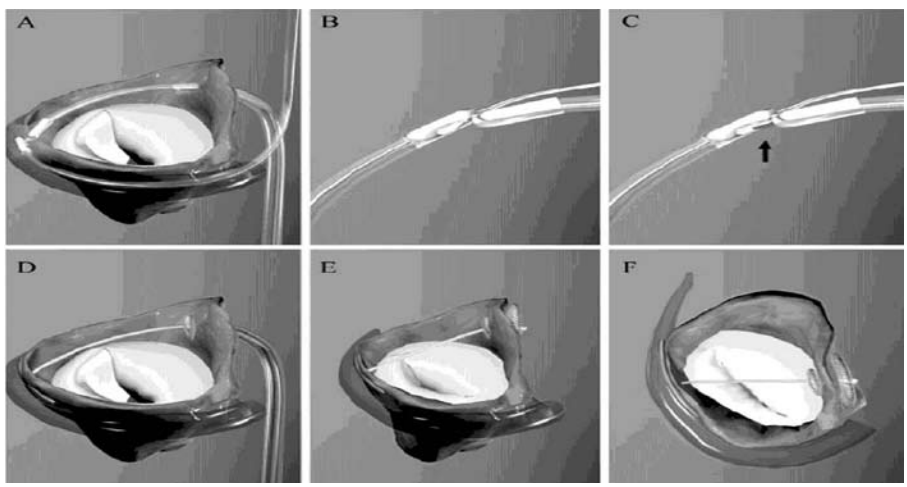
d. Viacor, Inc. device



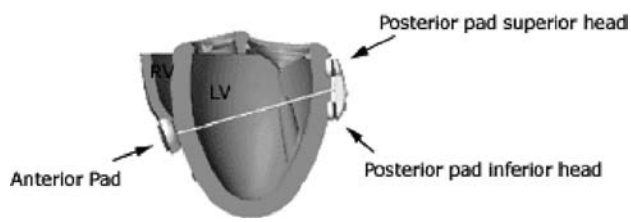
e. Viking percutaneous mitral valve annuloplasty device



f. Mitralign Annular Plication Device



g. Percutaneous Septal Sinus Shortening (PS3) device implant mode



h. Coapsys device

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