Review Paper

Percutaneous Treatment of Valvular Heart Disease: Catheter-Based Aortic Valve Replacement and Mitral Valve Repair Therapies

Ted Feldman, MD;[1] Howard C. Herrmann, MD;[2] Fred St. Goar, MD[3]
From Evanston Hospital, Evanston, IL;[1] the University of Pennsylvania, Philadelphia, PA;[2] and the Cardiovascular Institute, Mountain View, CA[3]
Address for correspondence: Ted Feldman, MD, Evanston Hospital, Cardiology Division–Burch 300, 2650 Ridge Avenue, Evanston, IL 60201
E-mail: tfeldman@enh.org

Until recently, percutaneous catheter therapy for valvular heart disease was limited to catheter balloon valvuloplasty for aortic, mitral, or pulmonic stenosis. A number of new approaches to percutaneous valve therapy are now developing rapidly, including methods for catheter-based valve replacement and repair. Stent-mounted valve prostheses have been successfully implanted in the pulmonic and aortic positions. These devices have been constructed using pericardial valve leaflets mounted inside balloon-expandable or self-expanding stents and have been used in patients who are high risk for valve replacement surgery. Percutaneous valve repair is also being developed for mitral regurgitation. Direct leaflet repair and percutaneous annuloplasty are being employed in clinical trials. All the percutaneous approaches are based on existing surgical techniques and offer less invasive alternatives. The era of percutaneous valve therapy has clearly arrived, and ongoing trials will define the clinical role for these new therapies. (AJGC. 2006;15:291–301) ©2006 Le Jacq

Therapy for valvular heart disease has been synonymous with surgical treatment for over 50 years. The era of heart valve replacement using cardiopulmonary bypass for intraoperative support signaled a revolution in therapy for a disease that afflicts hundreds of thousands of patients in the United States annually. Surgery has been remarkably effective at relieving symptoms of aortic and mitral valve disease and, in many instances, prolonging life.

At the same time, open heart surgery is highly invasive. The risks for patients who are good candidates for these therapies are substantial. As patients grow older and develop increasing numbers of comorbid conditions, the risks of valve replacement and valve repair operations increase further.[1–3] In addition to the goal of mitigating risk for open heart surgical procedures, the development of percutaneous therapies for coronary and peripheral vascular disease has stimulated the development of similar percutaneous approaches for valve lesions.

The first valve lesion to be treated successfully with percutaneous therapy was pulmonic stenosis, and pulmonic balloon valvuloplasty has become the principal therapy for this problem.[4] Other stenotic lesions have been successfully treated with balloons as well. Aortic stenosis in children and young adults is treated with balloon valvuloplasty as an initial (class 1) approach.[4,5] Mitral stenosis was first treated with a balloon catheter in 1982 by Inoue and colleagues.[6] For patients with predominant mitral stenosis and favorable valve leaflet morphology, percutaneous commissurotomy is the treatment of choice.[6–8]

Despite the availability of percutaneous therapies for stenotic lesions, regurgitant lesions have remained beyond the reach of catheter therapy until recently. Over the past few years, the development of percutaneous bioprosthetic stent-mounted artificial valve prostheses has emerged. In addition,

www.lejacq.com ID: 4880

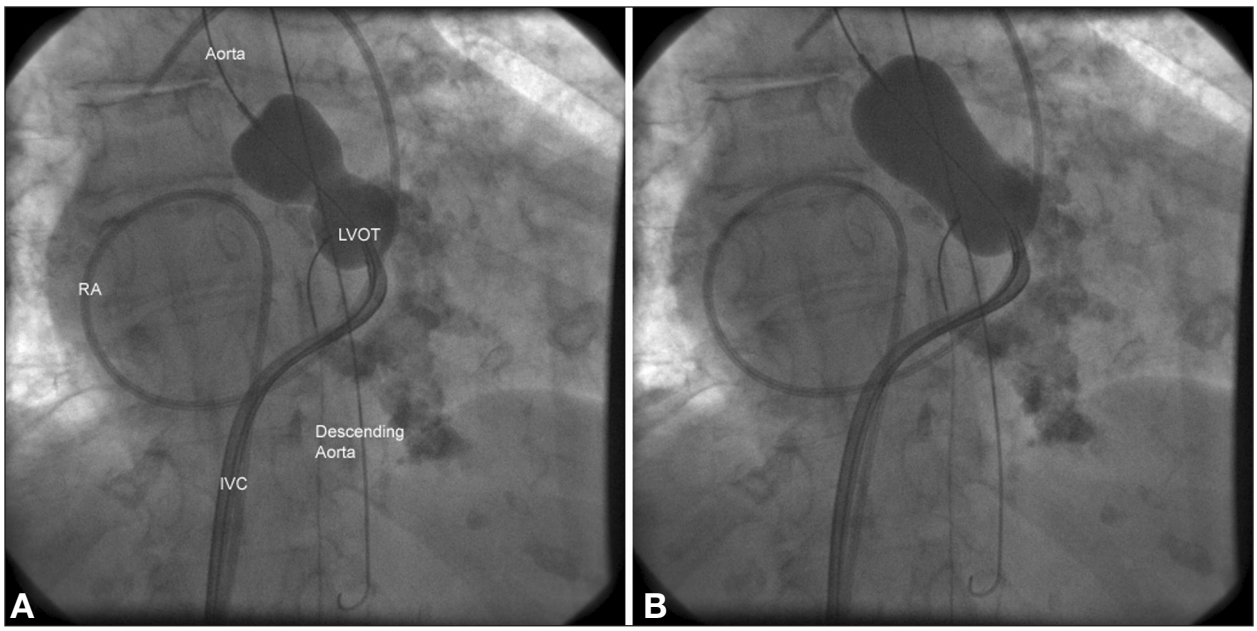

Figure 1. Fluoroscopic images from antegrade balloon aortic valvuloplasty. The balloon is passed over a guidewire that has been looped through the inferior vena cava (IVC), right atrium (RA), and across the atrial septum into the left atrium and left ventricle. (A) The balloon is positioned in the left ventricular outflow tract (LVOT). Calcifications can be seen indenting the center of the balloon. The distal portion of the balloon is in the aorta, and the guidewire loops through the aortic arch and into the descending aorta. (B) The balloon is fully inflated, deforming the calcified aortic leaflets to make them more mobile.

approaches to mitral valve repair for mitral regurgitation (MR) are beginning to develop. Leaflet repair using an adaptation of a surgical approach to plicate the free edges of the mitral leaflets together is in the midst of a large clinical trial in the United States. Annuloplasty via the coronary sinus is in phase 1 human trials. A number of novel methods for direct annuloplasty, and devices to help reduce MR using transpericardial or transatrial approaches, are also under development.

BALLOON AORTIC VALVULOPLASTY

Catheter-based options for aortic stenosis first appeared in the early 1980s with the advent of balloon aortic valvuloplasty (BAV) (Figure 1). BAV has been a highly successful therapy for children and young adults with aortic valve stenosis, resulting in both symptomatic relief and durable increases in the aortic valve area. Despite enthusiasm for BAV in older adult patients with aortic valve stenosis in the mid-1980s, the therapy has had disappointing medium- and long-term outcomes.[9,10] It has been demonstrated repeatedly that survival for patients with aortic valve stenosis is not increased by BAV and that restenosis occurs in the vast majority of patients within 6–24 months after therapy.[11,12]

Despite a lack of impact on long-term mortality, BAV remains a palliative therapy for many patients who are poor candidates for valve replacement surgery. The goal of therapy in older adults with aortic valve stenosis is often simply relief of symptoms. Octogenarian and nonagenarian patients with multiple comorbidities who are hospitalized repeatedly for congestive heart failure, and who are debilitated to the point that activities of daily living are highly compromised, may benefit from even short-term symptomatic relief. These patients highly value any level of clinical improvement that will enable them to avoid frequent hospitalizations, engage more fully in activities of daily living, and have relief of symptoms at rest. For this group of patients, the potential for improved symptoms with minimal procedural morbidity and a short hospital stay is highly attractive.[13,14]

It is not widely appreciated that aortic valve surgery in this group of patients is complicated by more than increased inhospital or 30-day surgical risk. While the upper decile of patients at high risk for aortic valve replacement (AVR) surgery may have hospital mortality in the range of 15%–18%, which is quite acceptable in this group, their 1-year survival is not substantially different from that of either untreated or BAV patients, with 1-year mortality as high as 40%–50%.

Furthermore, for this group of older, high-risk patients, quality of life is the major reason for

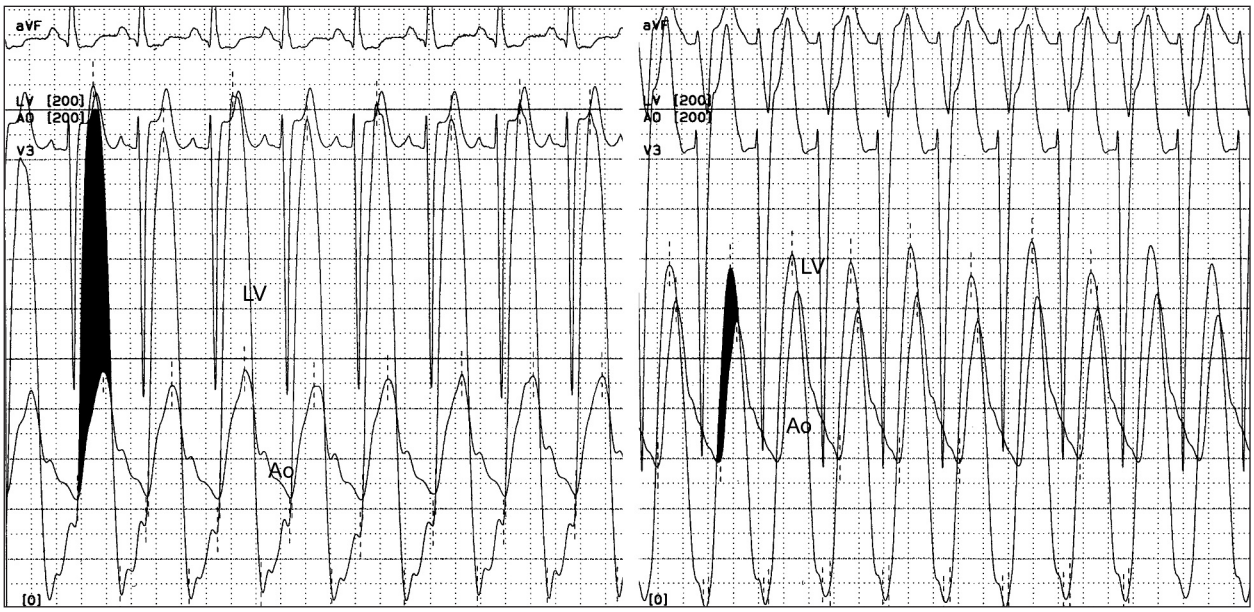

Figure 2. Hemodynamic pressure tracings recorded before and after balloon aortic valvuloplasty. On the left, the shaded portion of the figure shows a large pressure gradient. The mean gradient is 70 mm Hg, and the peak gradient is >100 mm Hg. The aortic (AO) pressure and left ventricular (LV) pressure are labeled. In the right-hand panel, after balloon inflations, the pressure gradient (shaded area) is diminished to both peak and mean values of 10 mm Hg. The peak LV systolic pressure has fallen, and the peak aortic systolic pressure has risen. The valve area in this case increased from 0.2 to 0.7 cm^2. The procedure was performed in an 88-year-old woman with class IV symptoms of congestive heart failure.

intervention of any kind. In conversations with elderly patients regarding management of aortic valve disease, they are relatively unconcerned about procedure mortality and highly concerned about the potential for stroke or prolonged disability during the recovery period. More than 50% of octogenarian and nonagenarian patients treated with AVR are discharged to nursing home facilities and may spend from 1 to 4 months undergoing rehabilitation.[15–17] Readmission to the hospital within 30 days of operation occurs in almost 20% of Medicare patients after AVR surgery. For patients with a limited life span, this represents a significant loss of quality of life. In addition, the stroke rate perioperatively in this group ranges between 5% and 15%, compared with ≤1% with BAV. Neurocognitive deficits occurring in conjunction with cardiopulmonary bypass may diminish the functional capacity of an additional substantial proportion of patients.[18,19]

Accordingly, BAV may represent an attractive alternate therapy for many of these older patients. Certainly, patients in the early octogenarian decade who are good candidates for AVR should have this therapy; however, many of these patients have a prior sternotomy or other comorbidities, including chronic lung disease, renal failure, chronic anemia, porcelain aorta, or multiple comorbidities. For these high-risk patients, BAV may offer excellent palliation for 1–2 years, with a hospital mortality of 5%–8%, and a length of stay of 1–2 days.[20] Length of stay for octogenarian patients after aortic valve surgery, in contrast, averages 2 weeks. Most BAV patients return to full activity immediately after discharge. Another variable is patient preference. It is common for older patients, especially those with a prior sternotomy, to want to avoid a major operation.

The best candidates for BAV are the ambulatory elderly. The prototypic patient is older than 80 years, with some comorbidity for valve surgery, but not yet hospital bound. Patients who have been hospitalized for days or weeks, who are "stuck" on pressors, or who are septic, are less likely to tolerate a BAV procedure.

The techniques for performing BAV include the conventional retrograde approach and the more recently utilized antegrade transseptal approach.[13] Both techniques have improved considerably since they were introduced in the 1980s. Most patients are palliated for 1–2 years after BAV. For many, this means that they avoid the repeated hospitalizations for congestive heart failure that are the most common current indication for this procedure (Figure 2).

In an attempt to improve the durability of results of BAV, Pederson has recently described focused neutron beam x-ray therapy for BAV

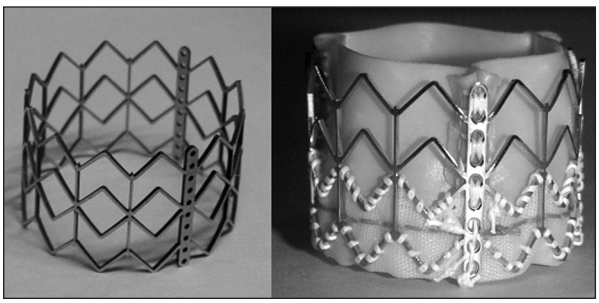

Figure 3. Percutaneous aortic valve prosthesis. This is an equine pericardial valve mounted on a balloon-expandable metal stent. The stent frame is seen on the left, and the completed bioprosthesis with the leaflet sewn into the frame is seen on the right. This is the Cribier-Edwards (Edwards Lifesciences, Irvine, CA) valve prosthesis.

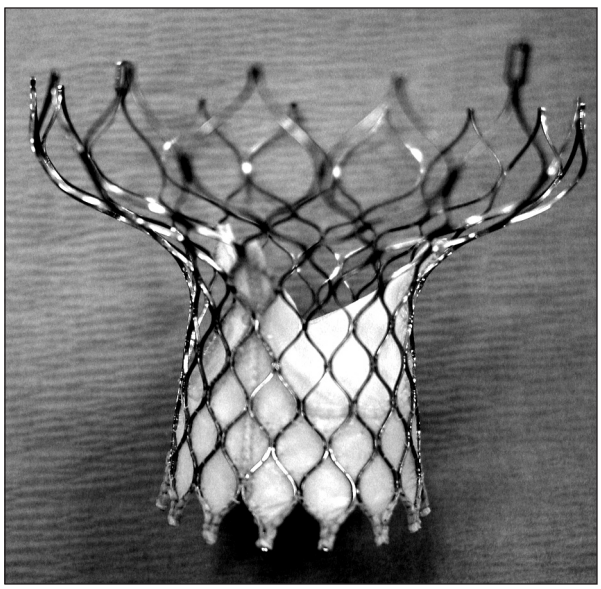

Figure 4. The CoreValve (CoreValve, Irvine, CA) self-expanding prosthesis. In contrast to the balloon-expandable device, this is sheathed to keep it compressed, and the metal frame expands as it is uncovered. A bioprosthetic valve is seen mounted within the metal frame. The distal portion of the stent expands to anchor the device in the aortic root.

patients.[21] Among patients who achieved a good initial result, a number have reached the 1-year postprocedure mark with a completely preserved postprocedure aortic valve area. This is a remarkable improvement in BAV results, which have been plagued by the occurrence of restenosis in the vast majority of patients.

It has been observed that statin therapy may diminish the progression of aortic stenosis. This has been seen in a number of observational studies but, to date, the single randomized trial is negative.[22] Unless a medical therapy for prevention of aortic stenosis is developed, the number of patients in need of valve therapy will grow substantially as the population ages. Accordingly, it remains unclear whether the incidence of senile calcific aortic stenosis will remain stable, decline, or increase in the next few decades.

In current practice, BAV is underutilized for the palliation of severe aortic stenosis in patients who are poor candidates for AVR surgery. Advanced age, porcelain aorta, prior sternotomy, low body mass index, and multiple organ system comorbidities remain important indications for the use of BAV in octogenarian and nonagenarian patients.

PERCUTANEOUS AORTIC VALVE REPLACEMENT

BAV plays only a limited role for older patients with severe aortic stenosis, and surgery with valve replacement is less than optimal for the octogenarian and older age group. In consequence, there has been interest for many years in developing percutaneously implantable aortic valve prostheses. Phase 1 clinical trials in patients with aortic stenosis are underway.

Andersen et al.[23] described a bioprosthetic leaflet valve mounted on a balloon-expandable metal stent in 1992. This was employed in a swine model. There was little further development until Bonhoeffer et al.[24,25] described implantation of a stent-mounted bioprosthetic valve as a pulmonic valve replacement in children with congenital heart disease. Bonhoeffer has now utilized this bioprosthesis in over 100 patients, with great success. This has clearly ushered in the era of percutaneous cardiac valve therapy. Bonhoeffer's valve is suited to the venous circulation, as it is made from a bovine jugular venous valve. He has treated patients with native pulmonic valve disease, and predominantly children and young adults with prior repair of congenital heart disease, in whom degenerated right-sided prosthetic valves have required repeated replacements.

The description of a stent-mounted bioprosthetic valve with implantation in patients by Cribier and colleagues[26] in 2001 has launched the field of percutaneous AVR (Figure 3). The initial experience with this device used an antegrade transseptal approach.[27] Successful valve implantation has resulted in immediate resolution of aortic valve stenosis, with restoration of normal hemodynamics and complete obliteration of the transaortic valve pressure gradient that is characteristic of aortic valve stenosis. The procedure was initially allowed by the French government only in patients who were turned down for open heart AVR by at

least two cardiovascular surgeons, and some of the early treated patients were in shock or undergoing cardiopulmonary resuscitation. The results of this experience had a high early mortality rate, but they nevertheless clearly demonstrated the feasibility of percutaneous AVR.

The technical challenges involved with transseptal antegrade implantation of this valve have led to efforts at AVR using a retrograde approach. Edwards Lifesciences (Irvine, CA) is developing the Cribier-Edwards valve, which has now been adapted for retrograde use.[28] A special 22F–24F arterial sheath is inserted via the femoral or iliac artery. (This eliminates many patients with significant peripheral vascular disease from consideration for this therapy.) Results from a phase 1 trial using the retrograde approach have recently been reported.[28] The retrograde approach offers greater technical simplicity than the antegrade approach. It has been used in over 30 patients, with greater ease of delivery and better patient hemodynamic tolerance than the antegrade approach. Important complications may still occur, including valve migration or embolization. This valve is compressed in a stent-mounted cage over a large balloon catheter. While the balloon is being inflated in the aortic valve annulus, the force of ventricular contraction may displace it. Accordingly, a temporary right ventricular pacemaker is used to create a heart rate of 200–220 bpm to effectively stop forward cardiac output. The gains are large when the procedure is successful, and there have been some stunning clinical outcomes, including immediate resolution of the transvalve pressure gradient and dramatic hemodynamic improvement.

An alternate technology uses the CoreValve (CoreValve, Irvine, CA), a self-expanding stent with a bioprosthetic valve mounted within it (Figure 4).[29] This system has been downsized to 18F during the initial human experience. Most of the procedures using this valve have been accomplished using percutaneous cardiopulmonary support to facilitate the procedures.

Percutaneous valve replacement for aortic stenosis is developing rapidly. The technology is suited for high-risk patients and will be particularly attractive in the elderly. Currently, somewhere between one third and two thirds of patients who meet American College of Cardiology/American Heart Association (ACC/AHA) guidelines for valve replacement for aortic stenosis do not undergo valve replacement procedures. The reasons for this involve both physician and patient bias. The availability of less-invasive therapies to treat symptomatic aortic stenosis in the elderly will greatly enhance treatment options for these patients.

MITRAL VALVE THERAPIES

Catheter-based approaches to treat mitral valve disease were first developed for mitral stenosis. Percutaneous transseptal mitral commissurotomy (PTMC) was first performed in 1982 by Inoue. PTMC is now the first choice of therapy for patients with mitral stenosis and pliable valve leaflets. PTMC has a large application internationally in countries where rheumatic heart disease remains endemic. Only a few thousand procedures are performed each year in the United States. Unfortunately, surgical mitral commissurotomy or valve replacement is still used for at least half of the patients with mitral stenosis who might otherwise be treated percutaneously, probably due to lack of familiarity with PTMC technique in the United States.

PTMC has a special role in the elderly with rheumatic mitral stenosis. Patients in their late 70s and beyond often present with highly deformed valves and severe pulmonary hypertension and multiple comorbid risks for surgical therapy. In this group, PTMC has an important role as a palliative therapy.[30]

Treatment of Mitral Regurgitation. For the past two decades, percutaneous therapy for valvular heart disease has been limited to balloon valvuloplasty for pulmonic, aortic, and mitral valve stenosis. The majority of patients in the United States with clinically important valvular heart disease, however, have regurgitant lesions. There have been no available percutaneous approaches to treat regurgitant lesions until recently. As many as 250,000 people in the United States have mitral regurgitation (MR). Over half of the more than four million Americans with dilated cardiomyopathy have some degree of functional MR. Over 50,000 mitral valve surgical procedures are performed annually—most for MR. Many of the patients with both degenerative and functional MR are poor candidates for surgery, most often due to associated poor left ventricular function or advanced age. Percutaneous methods for treating MR have the potential to offer a less invasive alternative to patients who are good surgical candidates and to create options for therapy for high-risk patients where none exist today.

A variety of advances have recently facilitated the development of methods to treat MR using catheter techniques via the percutaneous route. Most of these approaches are modifications of

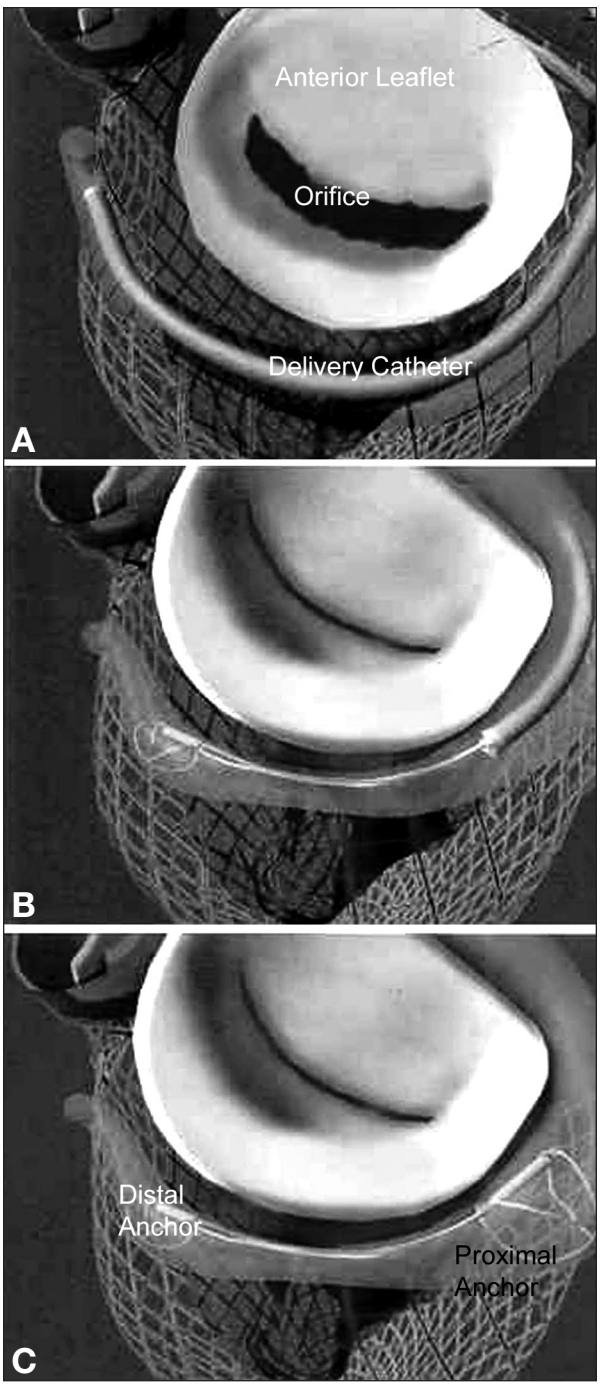

Figure 5. Schematic showing the route of delivery of a coronary sinus annuloplasty device. (A) The anterior leaflet of the mitral valve and mitral orifice are labeled. The delivery catheter is passed into the coronary sinus, which encircles the posterior leaflet of the mitral valve. (B) A wire device is seen anchored in the distal coronary sinus, and the catheter is withdrawn to both tension the device and ultimately expose the proximal anchor. The regurgitant orifice has been compressed by the tension exerted by the device. (C) The device has been delivered, with the distal and proximal anchors labeled, and the regurgitant orifice compressed from the lateral to the septal sides of the left ventricle.

established surgical therapies. The mainstay of surgical repair for MR has been annuloplasty. Rings that encircle the mitral annulus to varying degrees have been employed with great success for many years. A key feature of many of these devices is that they do not necessarily capture the circumference of the mitral annulus.

One percutaneous approach depends on recognition that the coronary sinus parallels the mitral annulus (Figure 5).[31,32] A device may be passed via the coronary sinus toward the great cardiac vein and thus encircle about two thirds to three fourths of the circumference of the mitral annulus, in a manner analogous to that achieved using surgical annuloplasty rings. The potential to reach around enough circumference of the coronary sinus to achieve a reduction in MR is the key element for this approach. A variety of devices, delivered via a transvenous jugular approach, can be placed into the coronary sinus (Figure 6 and Figure 7). Tension placed on the coronary sinus results in a decrease in the mitral annular circumference. In animal models, this has resulted in significant, sustained improvements in MR.

One of the animal models for the study of functional MR is an ovine paced-tachycardia cardiomyopathy.[33] Sheep can be paced at ventricular rates of 220 bpm, and will develop a myopathy with functional MR. The severity of the regurgitation is proportional to the duration of pacing. In this model, a coronary sinus-based device has effected a sustained diminution in the degree of MR.

Temporary intraoperative testing of some of these coronary sinus implants has been evaluated.[34,35] Patients taken for surgical mitral annuloplasty have had a percutaneous device placed while on the operating table. The degree of reduction in MR can be evaluated, then the device can be removed, and the planned surgical procedure completed. Preliminary work with two devices has shown improvements in MR, but not yet of a degree sufficient to consider using these devices for permanent implantation.

It has become clear after some preliminary work in autopsy specimens, and in limited temporary implantation in small numbers of patients, that the relationship of the coronary sinus to the mitral annulus in patients is highly variable compared with what has been observed in pre-clinical models. In addition, branches of the circumflex coronary artery may cross over or under the coronary sinus. Both of these factors are challenges to the development of mitral annuloplasty devices placed via this route.

Webb et al.[36] reported the first permanent human implantations of a coronary sinus annuloplasty device. The device uses two stents with a contractile connecting bridge between them to diminish the mitral annular circumference (Figure 7). Among five treated patients, the bridge fractured in three, without any clinical complications but with loss of efficacy. This has led to redesign of the device, and the trial has been resumed. It is clear that many problems will have to be solved before these technologies are ready for wide use.

Another approach to mitral annuloplasty that eliminates some of the challenges posed by the coronary sinus involves direct access to the left ventricle with placement of a device on the ventricular side of the mitral annulus. Access to the small space underneath the mitral leaflets via retrograde aortic catheterization is clearly technically difficult, but may be achieved using deflectable catheters. Anchoring of an annuloplasty device to the ventricular surface of the annulus via this route has been accomplished successfully in animal models.

A third approach to treating MR is via a transpericardial approach (Figure 8).[37] Patches can be placed on the epicardial surface, with a tensioning cable used to pull them together. This results in papillary muscle reorientation and lessens distortion of the left ventricular geometry caused by ventricular chamber dilation. Diminution of the septal-to-lateral dimension of the mitral annulus can be accomplished using a transpericardial delivery system with epicardial tensioning devices. Decreasing the septal–lateral dimension moves the posterior leaflet toward the septum, with resulting improved coaptation with the anterior leaflet.

Although the most common surgical mitral repair techniques involve annuloplasty, another basic approach is leaflet repair. One type of surgical leaflet repair involving plication of the free edges of the mitral leaflets to one another was developed by Alfieri and colleagues[38,39] in the early 1990s. Suturing together the free edge of the central segments of the leaflets was initially used by Alfieri for patients with mitral prolapse—frequently, bileaflet prolapse that could not be managed with other repair techniques. Plication of the leaflets results in a double orifice, or "bow-tie" orifice, which reduces the orifice area and also insures coaptation of the prolapsing segment. Alfieri and his colleagues have subsequently gone on to demonstrate that this technique can also be used successfully in patients suffering from functional MR.

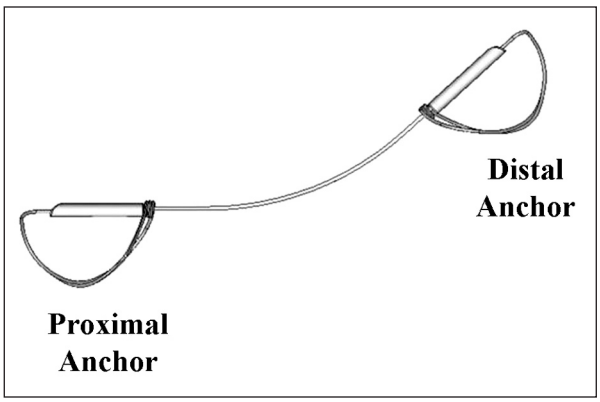

Figure 6. The Cardiac Dimensions (Kirkland, WA) Carillon coronary sinus mitral annuloplasty device. The two anchors are shown connected by a bridging element. As seen in Figure 5, the anchors are used to help the device exert tension on the circumference of the mitral annulus via the coronary sinus.

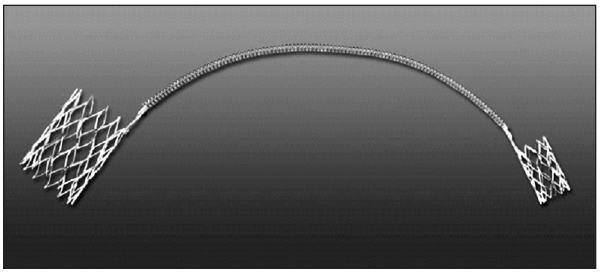

Figure 7. The Edwards Viking (Edwards Lifescience, Irvine, CA) coronary sinus annuloplasty device. In this case, self-expanding stents are used as the proximal (larger) and distal anchors. The bridge element between the two is a spring that is initially held open by bioabsorbable suture material in its interstices. After implantation, the material degrades, allowing the spring to exert tension on the coronary sinus and cause diminution of the circumference of the mitral annulus.

A method to achieve plication of the mitral leaflets and create a double orifice valve in this manner has been adapted to percutaneous use.[40] Via a transseptal guiding catheter, a metal clip can be navigated through the left atrium and into the mitral orifice, and then deployed on the mitral leaflets (Figure 9). This approach has been tested in an animal model and shown to yield similar results to the suturing of the leaflets in patients. A tissue bridge forms over the clip after a few months in the same manner as is seen after suturing of the leaflets.[41]

The percutaneous procedure is accomplished in patients using a large-caliber transseptal guide catheter. After standard transseptal puncture, the guide catheter is placed in the mid-left atrium. The mitral clip is delivered using a catheter with a multiaxial steering apparatus so that it can be

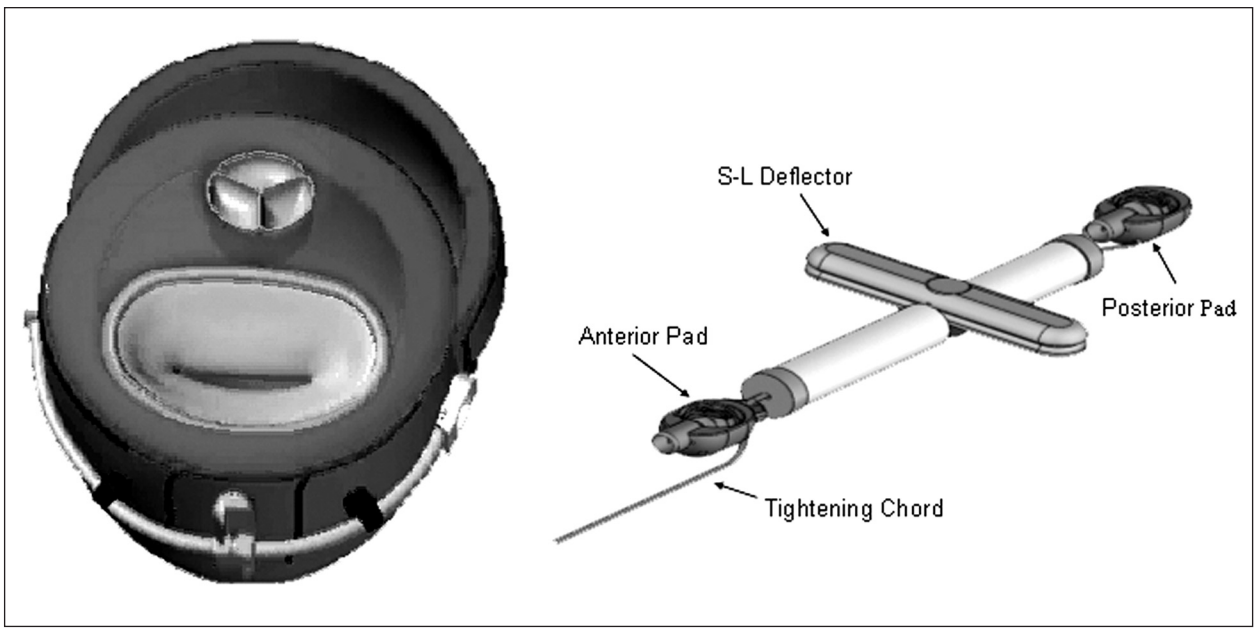

Figure 8. Transpericardial mitral annuloplasty device. The Myocor (Minneapolis, MN) Coapsys device is delivered via pericardial puncture. On the left, the device is seen on the epicardial surface of the heart, where it can exert pressure on the posterior mitral leaflet to compress the regurgitant orifice. On the right, the elements of the device are labeled. The two pads are attached to a septal-lateral (S-L) deflector that compresses the mitral valve to diminish the regurgitant orifice. This device is unique in that it also helps reorient the distorted papillary muscles and restore more normal left ventricular geometry.

maneuvered into the center of the mitral orifice in three dimensions. It is critical to place the device centrally, and oriented with the clip arms perpendicular to the line of mitral leaflet coaptation. The procedure is guided by a combination of fluoroscopic and echocardiographic imaging and requires transesophageal echocardiography. The clip can be placed, and the formation of a double orifice and reduction in MR can be evaluated immediately. If the MR jet is seen to be lateral or medial to the clip, the clip can be opened, the leaflets released, the clip repositioned, and the mitral leaflets regrasped to improve upon the results. In the event that adequate control of the MR cannot be achieved, a second clip may be added, or the first clip may be opened and removed from the patient.

A phase 1 clinical trial of the Evalve (Evalve, Menlo Park, CA) cardiovascular valve repair system (Endovascular Valve Edge-to-Edge Repair Study [EVEREST-I]) has been reported.[42] Surgical candidates with moderate-to-severe or severe MR (grade 3+ or 4+) with symptoms (or asymptomatic with ejection fraction <60% or left ventricular end-systolic dimension >45 mm) were included. Key exclusion criteria included ejection fraction <30%, left ventricular end-systolic dimension >55 mm, endocarditis, previous sternotomy, and rheumatic heart disease. The procedure uses general anesthesia, fluoroscopy, and echocardiographic guidance. A 24F guide catheter is positioned in the left atrium. The clip is centered over the mitral orifice, passed into the left ventricle, and pulled back to grasp the mitral leaflets. After verification that the MR is reduced, the clip is released.

Twenty-seven patients have been followed for 6 months. Clips were implanted in 24 patients. There were no procedural complications; there were four 30-day major adverse events: partial clip detachment in three patients, who underwent elective valve surgery, and one with a postprocedure stroke, which resolved at 1 month. Three additional patients had surgery for unresolved MR, leaving 18 patients free from surgery. In 13 of 14 patients with reduction of MR to grade 2+ or less after 1 month, the reduction was maintained at 6 months. Patients who required subsequent surgery had elective mitral valve repair or intended replacement.

In the event that a clip is not ultimately placed, mitral valve surgery can be undertaken electively without any loss of the options for either surgical repair or mitral valve replacement. To date, the procedure has been accomplished safely, and a significant reduction in MR has been achieved in the majority of patients treated. The average length of hospital stay is less than two nights. Management of the femoral venous puncture has not been any more challenging than for other

Figure 9. The Evalve (Menlo Park, CA) MitraClip. The left and center panels are schematics of the clip. On the left, the clip arms are open, and gripping elements can be seen. The leaflets are engaged between the gripping elements and the clip arms, and then the clip arms are closed as seen in the center figure. A photograph of the device, on the right, shows the polyester covering and the guide catheter system. This device is delivered into the mitral orifice via a transseptal route.

valve interventional therapies via the transseptal route. Further study is clearly necessary to define the role of this therapy relative to mitral valve repair using surgical methods. It is clear that the ideal patient population for this procedure will be defined by ongoing trial experience.

In the EVEREST-I trial there was a clear referral bias for elderly patients who were poor candidates for mitral valve surgery. It is intuitive that percutaneous therapies would be desirable for high-risk patients. Nonetheless, the EVEREST-II phase 2 randomized trial is a comparison with surgical valve repair or valve replacement. A number of factors are interesting about this trial design. There are no prospective, core laboratory evaluated, intention-to-treat trials of mitral repair or replacement therapy in the surgical literature. Thus, of the population of patients for whom repair is intended, the proportion in whom replacement is ultimately performed is not clearly defined. The result of mitral repair in terms of the degree of reduction of MR has never been assessed using objective criteria for MR grading and a core laboratory.[43] Thus, the randomized EVEREST-II trial will be groundbreaking not only in the development of percutaneous therapy, but also in defining the contemporary results of mitral valve surgery. Ultimately, determining the specific applicability of this technology, whether for elderly patients who are at high risk for surgical therapy or younger patients with severe, yet asymptomatic mitral insufficiency, will require extensive investigative trials and clinical experience.

The development of these technologies for percutaneous mitral valve repair will clearly evolve rapidly. Over the long term, the potential for a variety of methods to be used in special patient populations, or possibly in combination, will be defined. Specific, differing therapies for dilated cardiomyopathy with functional MR, ischemic MR, or mitral valve prolapse will be developed.[44]

Greater understanding among cardiology practitioners of mitral valve pathoanatomy and the specific methods needed to repair the various pathologies is clearly important. Development of these new technologies will benefit from the input of the various interventional, surgical, and imaging cardiovascular specialities. In the meantime, we are on the threshold of an exciting era in catheter therapy for valvular heart disease. Percutaneous valve repair and replacement are realities in clinical research, and likely also soon in clinical practice. These approaches are already attractive for use in older patients, and will hopefully make treatment available to many who now have no options and make it less invasive for many others.

References

1 Levinson JR, Akins CW, Buckley MJ, et al. Octogenarians with aortic stenosis. Outcome after aortic valve replacement. *Circulation.* 1989;80(3 pt 1):I49–I56.

2 Kolh P, Kerzmann A, Lahaye L, et al. Cardiac surgery in octogenarians; peri-operative outcome and long-term

results. *Eur Heart J.* 2001;22:1235–1243.
3 Burr LH, Jamieson WR, Munro AI, et al. Porcine bioprostheses in the elderly: clinical performance by age groups and valve positions. *Ann Thorac Surg.* 1995;60(2 suppl): S264–S269.
4 Bonow RO, Carabello B, de Leon AC Jr, et al. Guidelines for the management of patients with valvular heart disease: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). *Circulation.* 1998;98:1949–1984.
5 Feldman T, Chiu YC, Carroll JD. Catheter balloon dilatation for discrete subaortic stenosis in the adult. *Am J Cardiol.* 1987;60:403–405.
6 Inoue K, Owaki T, Nakamura T, et al. Clinical application of transvenous mitral commissurotomy by a new balloon catheter. *J Thorac Cardiovasc Surg.* 1984;87:394–402.
7 Feldman T, Herrmann HC, Inoue K. The technique of percutaneous transvenous mitral commissurotomy using the Inoue balloon catheter. *Cathet Cardiovasc Diagn.* 1994;suppl 2:26–34.
8 Feldman T. Hemodynamic results, clinical outcome and complications of Inoue balloon mitral valvotomy. *Cathet Cardiovasc Diagn.* 1994;2:2–7.
9 Otto CM, Mickel MC, Kennedy JW, et al. Three-year outcome after balloon aortic valvuloplasty. Insights into prognosis of valvular aortic stenosis. *Circulation.* 1994;89:642–650.
10 Lieberman EB, Bashore TM, Hermiller JB, et al. Balloon aortic valvuloplasty in adults: failure of procedure to improve long-term survival. *J Am Coll Cardiol.* 1995;26:1522–1528.
11 O'Keefe JH Jr, Vlietstra RE, Bailey KR, et al. Natural history of candidates for balloon aortic valvuloplasty. *Mayo Clin Proc.* 1987;62:986–991.
12 Feldman T, Glagov S, Carroll JD. Restenosis following successful balloon valvuloplasty; bone formation in aortic valve leaflets. *Cathet Cardiovasc Diagn.* 1993;29:1–7.
13 Sakata Y, Sayed Y, Salinger MH, et al. Percutaneous balloon aortic valvuloplasty: antegrade transseptal vs. conventional retrograde transarterial approach. *Catheter Cardiovasc Interv.* 2005;64:314–321.
14 Feldman T. Transseptal antegrade access for aortic valvuloplasty. *Catheter Cardiovasc Interv.* 2000;50:492–494.
15 Goodney PP, Stukel TA, Lucas FL, et al. Hospital volume, length of stay, and readmission rates in high-risk surgery. *Ann Surg.* 2003;238:161–167.
16 Sharony R, Grossi EA, Saunders PC, et al. Minimally invasive aortic valve surgery in the elderly: a case-control study. *Circulation.* 2003;108(suppl 1):II43–II47.
17 Sundt TM, Bailey MS, Moon MR, et al. Quality of life after aortic valve replacement at the age of >80 years. *Circulation.* 2000;102(19 suppl 3):III70–III74.
18 Zimpfer D, Czerny M, Kilo J, et al. Cognitive deficit after aortic valve replacement. *Ann Thorac Surg.* 2002;74:407–412.
19 Newman MF, Kirchner JL, Phillips-Bute B, et al., for the Neurological Outcome Research Group and the Cardiothoracic Anesthesiology Research Endeavors Investigators. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. *N Engl J Med.* 2001;344:395–402.
20 Agarwal A, Kini AS, Attanti S, et al. Results of repeat balloon valvuloplasty for treatment of aortic stenosis in patients aged 59 to 104 years. *Am J Cardiol.* 2005;95:43–47.
21 Pederson WR, Pence D, Knickelbine T, et al. Radiation following percutaneous balloon aortic valvuloplasty to prevent restenosis (RADAR Pilot). *Circulation.* 2004;110(suppl III):440.
22 Cowell SJ, Newby DE, Prescott RJ, et al., for the Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) Investigators. A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. *N Engl J Med.* 2005;352:2389–2397.
23 Andersen HR, Knudsen LL, Hasenkam JM. Transluminal implantation of artificial heart valves. Description of a new expandable aortic valve and initial results with implantation by catheter technique in closed chest pigs. *Eur Heart J.* 1992;13:704–708.
24 Bonhoeffer P, Boudjemline Y, Saliba Z, et al. Percutaneous replacement of pulmonary valve in a right-ventricle to pulmonary-artery prosthetic conduit with valve dysfunction. *Lancet.* 2000;356:1403–1405.
25 Lutter G, Ardehali R, Cremer J, et al. Percutaneous valve replacement: current state and future prospects. *Ann Thorac Surg.* 2004;78:2199–2206.
26 Cribier A, Eltchaninoff H, Bash A, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. *Circulation.* 2002;106:3006–3008.
27 Cribier A, Eltchaninoff H, Tron C, et al. Early experience with percutaneous transcatheter implantation of heart valve prosthesis for the treatment of end-stage inoperable patients with calcific aortic stenosis. *J Am Coll Cardiol.* 2004;43:698–703.
28 Webb JG, Chandavimol M, Thompson CR, et al. Percutaneous aortic valve implantation retrograde from the femoral artery. *Circulation.* 2006;113:842–850.
29 Grube E, Laborde JC, Zickmann B, et al. First report on a human percutaneous transluminal implantation of a self-expanding valve prosthesis for interventional treatment of aortic valve stenosis. *Catheter Cardiovasc Interv.* 2005;66:465–469.
30 Feldman T, Carroll JD, Isner JM, et al. Effect of valve deformity on results and mitral regurgitation after Inoue balloon commissurotomy. *Circulation.* 1992;85:180–187.
31 Maniu CV, Patel JB, Reuter DG, et al. Acute and chronic reduction of functional mitral regurgitation in experimental heart failure by percutaneous mitral annuloplasty. *J Am Coll Cardiol.* 2004;44:1652–1661.
32 Byrne MJ, Kaye DM, Mathis M, et al. Percutaneous mitral annular reduction provides continued benefit in an ovine model of dilated cardiomyopathy. *Circulation.* 2004;110:3088–3092.
33 Byrne MJ, Power JM, Alferness CA, et al. Percutaneous mitral annular reduction: a novel approach to the management of heart failure associated mitral regurgitation. *Circulation.* 2003;108:S2042.
34 Liddicoat JR, Mac Neill BD, Gillinov AM, et al. Percutaneous mitral valve repair: a feasibility study in an ovine model of acute ischemic mitral regurgitation. *Catheter Cardiovasc Interv.* 2003;60:410–416.
35 Oesterle SN, Gillinov AM, Chin CH, et al. Percutaneous catheter-based mitral valve repair [abstract]. *J Am Coll Cardiol.* 2002;39(5 suppl A):866. Abstract 432A.
36 Webb JG, Harnek J, Munt BI, et al. Percutaneous transvenous mitral annuloplasty: initial human experience with device implantation in the coronary sinus. *Circulation.* 2006;113:851–855.
37 Grossi EA, Saunders PC, Woo J, et al. Intraoperative effects of the Coapsys annuloplasty system in a randomized

evaluation (RESTOR-MV) of functional ischemic mitral regurgitation. *Ann Thorac Surg.* 2005;80:1706–1711.

38 Alfieri O, Elefteriades JA, Chapolini RJ, et al. Novel suture device for beating-heart mitral leaflet approximation. *Ann Thorac Surg.* 2002;74:1488–1493.

39 Alfieri O, Maisano F, DeBonis M, et al. The edge-to-edge technique in mitral valve repair: a simple solution for complex problems. *J Thorac Cardiovasc Surg.* 2001;122:674–681.

40 St Goar FG, James FI, Komtebedde J, et al. Endovascular edge-to-edge mitral valve repair: short-term results in a porcine model. *Circulation.* 2003;108:1990–1993.

41 Fann JI, St Goar FG, Komtebedde J, et al. Off-pump edge-to-edge mitral valve technique using a mechanical clip in a chronic model. *Circulation.* 2003;108(supp IV):493.

42 Feldman T, Wasserman HS, Herrmann HC, et al. Percutaneous mitral valve repair using the edge-to-edge technique: six-month results of the EVEREST Phase I Clinical Trial. *J Am Coll Cardiol.* 2005;46:2134–2140.

43 Zoghbi WA, Enriquez-Sarano M, Foster E, et al. American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr.* 2003;16:777–802.

44 Feldman T. Percutaneous valve repair and replacement: challenges encountered, challenges met, challenges ahead [editorial]. *Circulation.* 2006;113:771–773.