The rationale for the development of a transcatheter mitral valve implantation (tMVI) procedure, either percutaneous or via minimally invasive surgery (MIS), arose from consideration of several key surgical concepts. First, mitral valve replacement is the most effective modality and the gold standard procedure for reliably reducing mitral regurgitation (MR). The efficacy and risks of mitral valve replacement are well understood, but include significant morbidity and mortality due to the incision, as well as the need for cardiopulmonary bypass. The benefits of surgical mitral valve repair relative to replacement in young patients with degenerative disease are much less apparent in older, higher-risk patients. Finally, it is becoming increasingly clear that percutaneous approaches to mitral repair are more limited than surgical techniques and are unlikely to achieve equal efficacy. This article will review and support these concepts, generating a rationale for the development of MIS-tMVI, and describe early investigations in this emerging field.

SURGICAL REPLACEMENT VERSUS REPAIR

One of the most important benefits of mitral valve repair when compared to replacement is the perception that it will result in better survival due to improved left ventricular remodeling. However, there has never been a randomized comparison of repair and replacement; hence, observational comparisons are limited by differences in patient baseline characteristics and comorbid conditions.

One recent study matched 322 mitral valve repair patients to an equal number of valve replacement patients using propensity scoring. With a median follow-up of 3.4 years, there was a modest survival benefit associated with repair, although freedom from reoperation was two-fold higher with replacement. Importantly, only 15% of these patients had an ischemic etiology. Gillinov and colleagues compared patients with ischemic MR, matching 397 repair patients with 85 replacement subjects. Patients receiving valve replacement had a higher New York Heart Association functional class and more severe MR. After adjusting for differences in baseline characteristics, the patients with the most complex and severe conditions had no survival benefit at 7 years from mitral valve repair compared with replacement.

The surgical literature offers several additional reasons to question the relative benefit of repair versus replacement. In one of the first published studies by...
Enriquez-Sarano and colleagues, the most frequently utilized valve was the older Starr-Edwards prosthesis (Edwards Lifesciences, Irvine, CA). In addition, operations in this series were performed between 1980 and 1990, before there was a general understanding of the importance of preserving the chordal apparatus to limit the adverse late left ventricular remodeling associated with replacement. In a recent randomized study, complete retention of the mitral subvalvular apparatus during mitral valve repair improved early left ventricle (LV) chamber size and resulted in more favorable LV remodeling compared to even partial posterior leaflet preservation (Figure 1). It is for these reasons that a randomized study sponsored by the National Institute of Health has recently been initiated to compare outcomes in patients with severe ischemic MR after mitral valve repair versus mitral valve replacement with complete subvalvular preservation.

Possibly the most important weakness of mitral valve repair relates to the risk of recurrent MR. Most surgical series report a high freedom from reoperation, but rarely include an independent echocardiographic laboratory assessment of MR recurrence. For example, in one large series of 649 repairs for degenerative disease, the 10-year freedom from reoperation was 95%, but 19% of patients had recurrent severe (3–4+) MR. Others have reported rates of moderately severe (3+) and severe (4+) MR in 35% of patients at 10 years. In patients with ischemic etiology, the overall survival, as well as the rate of recurrent MR, is even worse. In a recent study from the Cleveland Clinic of 290 patients with ischemic MR undergoing coronary artery bypass grafting and repair, the rate of severe (3–4+) MR was 9% at 1 year and increased to 20% by 5 years of follow-up.

**PERCUTANEOUS MITRAL VALVE REPAIR VERSUS SURGERY**

Although the results with surgery for MR are acceptable, the risks of surgery, particularly if one includes morbidity, as well as patient preference, have stimulated attempts to develop less invasive solutions. These approaches generally fall into two major categories: (1) those that attempt to remodel the posterior mitral annulus either directly or via the coronary sinus, and (2) edge-to-edge leaflet repair. Early first-in-man and phase 1 results with these devices have documented improvement in selected patients, but are unlikely, in this author’s view, to solve the problem of MR for most patients.

Concerns relative to coronary sinus devices include theoretical issues, in addition to the usual safety and efficacy variables. Experimental investigations in the ischemic sheep model have demonstrated that even with good MR reduction, adverse LV remodeling may continue, thereby limiting any initial benefit. In humans, partial or only posterior annuloplasty repairs are associated with very high rates of recurrent MR. From a safety standpoint, early device failures, as well as coronary artery compression and compromise, have been reported. The latter may occur due to the presence of the left circumflex or a diagonal branch coronary artery, which traverses between the coronary sinus and mitral annulus in up to 80% of patients. Finally, because the coronary sinus is not coplanar with the mitral annulus and exhibits great individual variability, it is difficult to obtain substantial MR reduction in many patients.

There are also concerns with edge-to-edge clip mitral valve repair. Although good results have been obtained in selected patients, there remain concerns about the nonanatomic nature of the repair and long-term efficacy in the absence of a concomitant ring annuloplasty. The initial safety profile has been good, but partial clip detachments have occurred in a small percentage of patients. Whether the improvement in MR is as good as surgery will soon be answered by a completely enrolled randomized trial.

Overall, it is likely that some patients will be able to benefit from a percutaneous approach to MR. However, many hurdles remain to be overcome, including procedure complexity, learning curve issues, patient selection, recognition and treatment of unique complications, and demonstration of comparative efficacy to surgery.
TRANSCATHETER MITRAL VALVE IMPLANTATION

Based on the previous discussion, it should be clear that surgeons have more robust repair techniques in their toolbox than are available with current percutaneous devices. Nonetheless, surgery continues to be associated with significant morbidity and mortality. In a study of 13,614 elective operations for MR from the Society of Thoracic Surgery database, operative mortality was 2.12% with a combined mortality and morbidity of 11% to 16%, depending on experience. Readmission for postoperative complications is particularly common in elderly patients, occurring in more than 20% of Medicare-aged patients (≥65 years). Finally, the risks of surgery increase with age to as high as 17% mortality and 36% morbidity in patients older than 80 years (Figure 2). Mitral valve replacement with current-generation bioprostheses and complete valve-sparing techniques can offer better MR reduction than repair, with similar survival in higher-risk patients. For these reasons, it is important to develop a less-invasive, valve-sparing means of performing a mitral valve replacement.

Several companies are attempting to develop percutaneous or minimally invasive mitral valve replacement devices. Most utilize a stent-based bioprosthesis inserted transseptally or transapically. Lutter and colleagues have published their initial experience utilizing a transapical, off-pump, porcine, self-expanding stent prosthesis in pigs. Although initial success was described, 7 of 8 animals died due to paravalvular leaks, suboptimal positioning, or failure of fixation. The potential for impingement and obstruction by a stent prosthesis on the left ventricular outflow tract is a theoretical concern.

Endovalve, Inc. is developing a mitral valve replacement system initially designed for insertion during an MIS procedure (Figure 3). The device is a foldable (non-stent) nitinol structure that attaches to the native valve apparatus with anatomically appropriately designed gripper technology and is fully valve sparing. The prosthesis includes a ring and bioprosthetic leaflets with a foldable tripod frame. It has integrated gripper features for fixation and attachment in the beating heart. The system is introduced via a catheter directly into the left atrium through a right minithoracotomy, with a specially designed delivery device and removable cables that allow contraction, repositioning, and release. A sewn fabric skirt provides perivalvular sealing.

Initial prototypes of the Endovalve prosthesis have undergone bench testing for hemodynamic assessment and flow visualization. In vivo sheep implants have demonstrated fixation, normal valve function, and lack of left ventricular outflow tract obstruction and MR. Detailed final design is underway prior to formal animal verification, which will be followed by clinical validation. A subsequent truly percutaneous delivery catheter using the same valve design is planned for later development.

CONCLUSION

The clinical advantages of MIS-tMVI are clear. This technology can avoid cardiopulmonary bypass and sternotomy, reduce MR as effectively as with surgery, take advantage of the improving durability of bioprosthetic leaflets, and is fully valve sparing. For these reasons, it has the potential to become the procedure of choice for high-risk patients with symptomatic MR.

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