Percutaneous Transvenous Mitral Annuloplasty
Initial Human Experience With Device Implantation in the Coronary Sinus

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Background—Mitral annuloplasty is the most common surgical procedure performed for ischemic mitral regurgitation (MR). Surgical mitral annuloplasty is limited by morbidity, mortality, and MR recurrence. We evaluated the safety and feasibility of a transvenous catheter-delivered implantable device to provide a percutaneous alternative to surgical mitral annuloplasty.

Methods and Results—Five patients with chronic ischemic MR underwent percutaneous transvenous implantation of an annuloplasty device in the coronary sinus. Implantation was successful in 4 patients. Baseline MR in the entire group was grade 3.0/4.0 and was reduced to grade 1.6/4.0 at the last postimplantation visit when the device was intact or the last postprocedural visit in the patient in whom the device was not successfully implanted. Separation of the bridge section of the device occurred in 3 of 4 implanted devices and was detected at 28 to 81 days after implantation. There were no postprocedural device-related complications.

Conclusions—Percutaneous implantation of a device intended to remodel the mitral annulus is feasible. Initial experience suggests a possible favorable effect on MR. Percutaneous transvenous mitral annuloplasty warrants further evaluation as a less invasive alternative to surgical annuloplasty. (Circulation. 2006;113:851-855.)

Key Words: annuloplasty ■ coronary sinus ■ heart failure ■ mitral valve ■ regurgitation

Mitral regurgitation (MR) is common after myocardial infarction and may lead to progressive ventricular and annular dilation, worsening regurgitation, and heart failure. MR severity is an independent predictor of prognosis in patients with ischemic heart disease, even when MR is moderate or mild, particularly in the presence of congestive failure. When MR is severe, prognosis is poor, even when asymptomatic. MR as a consequence of ischemic disease most often occurs despite the presence of structurally normal mitral valve leaflets. Left ventricular dysfunction or remodeling can result in annular dilation or papillary muscle displacement with incomplete mitral leaflet apposition or restricted mitral leaflet motion.

Surgical approaches to MR include mitral valve replacement and repair. Recent literature favors early repair in structural MR when feasible or in patients with ischemic MR and symptomatic heart failure. However, morbidity, mortality, and late recurrent MR limit widespread application of surgical repair. Although surgical mitral repair may be sophisticated and complex, most repairs currently consist of simple annuloplasty.

Should percutaneous repair prove efficacious and safe, then it might have a potential role early in the natural history of MR. The proximity of the coronary sinus to the mitral annulus has been the basis for a number of approaches to percutaneous transvenous mitral valve annuloplasty (PTMA). Animal studies have demonstrated the potential to remodel the mitral annulus, reduce mitral anteroposterior diameter, improve leaflet coaptation, and reduce regurgitation. Temporary intraprocedural placement of a coronary sinus annuloplasty device in humans has been shown to have the potential to decrease mitral annular diameter and insufficiency. We report here the first experience with PTMA device implantation in humans.

Methods

Study Design

The primary objective of this study was to evaluate the acute safety of PTMA in patients with chronic ischemic MR. Patients were enrolled at 2 sites, St Paul’s Hospital (Vancouver, British Columbia, Canada) and Lund University Hospital (Lund, Sweden). The protocol was approved by the appropriate institutional ethics committees.
Boston Scientific Inc) was advanced into the distal vessel. A catheter. An exchange wire (0.035 in [260 cm], Magic Torquewire, Heparin (50 U/kg IV) was administered after jugular puncture. on clopidogrel 75 mg daily for 3 months and aspirin indefinitely. clopidogrel 300 mg and aspirin 325 mg and subsequently continued patients under local anesthesia. Patients were premedicated with The procedure was performed in the catheterization laboratory in

Figure 1. Top, The Viking percutaneous mitral valve annuloplasty device is constructed of nitinol and consists of a larger proximal anchor, a flexible shortening bridge segment, and a smaller distal anchor. Bottom, The delivery system consists of an over-the-wire inner catheter on which is mounted the compressed implant and an outer restraining sheath. The sheath is retracted with a thumb sliding mechanism that sequentially releases the self-expanding distal and then the proximal anchor.

Informed consent was obtained. Candidates had functional MR ≥2+ on a scale of 4+ in the setting of prior myocardial infarction. Exclusion criteria included left ventricular ejection fraction <30%, structural mitral valve disease, mitral annular calcification, prior endocarditis or mitral surgery, creatinine >2.0 mg/dL, coronary sinus pacing leads, anticipated revascularization, inability to take aspirin or clopidogrel, or a life expectancy <1 year.

Device Description
The Percutaneous Mitral Annuloplasty System (Viking, Edwards Lifesciences Inc) consists of a 12F-outer-diameter guide catheter and dilator, a 9F delivery catheter, and a nickel-titanium alloy (nitinol) implant (Figure 1). The implant itself is made up of 3 sections: a distal self-expanding anchor, a springlike “bridge,” and a proximal self-expanding anchor. The distal anchor is deployed in the great cardiac vein; the proximal anchor is deployed in the proximal coronary sinus. The bridge has shape-memory properties that result in shortening forces at body temperature. The anchors draw the proximal coronary sinus and distal great cardiac vein together while the bridge section tenses and straightens, indirectly displacing the posterior annulus anteriorly and reducing mitral annulus diameter and septal-lateral distance.

Procedure
The procedure was performed in the catheterization laboratory in patients under local anesthesia. Patients were premedicated with clopidogrel 300 mg and aspirin 325 mg and subsequently continued on clopidogrel 75 mg daily for 3 months and aspirin indefinitely. Heparin (50 U/kg IV) was administered after jugular puncture.

The coronary sinus was cannulated with a standard 6F coronary catheter. An exchange wire (0.035 in [260 cm], Magic Torquewire, Boston Scientific Inc) was advanced into the distal vessel. A measurement catheter (Royal Flush, Cook Inc) with radiopaque 1-cm markers was advanced over the wire to the level of the great cardiac vein. The coronary venous system was opacified by injections through the measurement catheter, the guiding catheter, or a catheter placed in the left coronary artery. The length of the vessel available for device implantation was determined by counting the radiopaque markers, thus avoiding underestimation of vessel length as a result of foreshortening of the coronary veins on the fluoroscopic image. Vessel diameter was determined by calibration against the known diameter of the angiographic catheter using standard catheterization laboratory quantitative angiographic software (Figure 2).

A suitable device was selected on the basis of the measured length and diameter of the target segment. A range of devices were available. The 12F guiding catheter was advanced over a guidewire well into the coronary sinus. The device delivery catheter was then passed over the wire, through the guiding catheter, and into the coronary venous system. The distal anchor was placed in the desired location using radiopaque markers on the delivery catheter, previously identified landmarks, retrograde injections through the guiding catheter, and left coronary arterial injections. Once correctly positioned, the distal anchor was released by retracting the outer restraining sheath with the thumb slider mechanism on the delivery catheter handle. After release of the distal anchor, slack was removed from the bridge element by withdrawing and tensioning the delivery catheter. With the proximal anchor correctly positioned just within the coronary sinus ostium, the restraining outer sheath was completely retracted. The delivery catheter and coaxial wire were removed (Figure 3).

Postprocedural Evaluation
Patients were evaluated at baseline, 24 hours, and 30, 90, and 180 days with a clinical examination, chest x-ray, and transthoracic echocardiogram. Creatine kinase and creatine kinase-MB were measured every 8 hours for 24 hours after the procedure. Coronary angiography was performed before the procedure and 3 months after implantation. Transesophageal echocardiograms were obtained before the procedure and at 3 months. Echocardiograms were reviewed by an independent core laboratory (Cardiovascular Research Institute, Washington, DC). The authors had full access to the data and
Results

Two clinical sites enrolled 5 patients with chronic, ischemic MR and normal valve leaflets. Age was $67 \pm 10$ years; 3 were male, and 2 were female.

Device implantation was successful in 4 of 5 patients. In 1 patient (patient 2), the device could not be advanced fully into the coronary sinus because of difficulty in obtaining coaxial guide position. Attempts to implant the device led to wire perforation of the anterior interventricular vein and pericardial effusion. A repeated attempt 1 month later was uneventful but also unsuccessful. A second patient developed transient atrial fibrillation during cannulation of the coronary sinus.

Positioning of the distal anchor was adequately assessed with the aid of fluoroscopic landmarks and left coronary artery injections. Visible shortening of the coronary sinus system was evident during device tensioning before proximal anchor release. In all patients who received implants, the anchors were correctly placed at the desired locations. Fluoroscopy time was 36±22 minutes, and contrast use was 312±95 mL.

At the 3-month follow-up, all patients remained alive. There was 1 late death (day 148) caused by progressive heart failure. This patient was considered a nonsurgical candidate because of morbid obesity and other comorbidities. Postmortem examination showed a well-positioned device, a patent coronary sinus with complete neointimal coverage, and a patent circumflex artery.

Coronary angiograms were obtained at 3 months in the other 3 patients who received implants. There was no evidence of compromise of the circumflex coronary artery as a result of the device implanted in the adjacent great cardiac vein. Coronary sinus patency was documented in all patients.

Separation of the nitinol bridge segment was documented in 3 of 4 patients who had received implants on routine follow-up chest radiographs at 22, 28, and 81 days. Migration of the anchors was not observed. Although there were no adverse clinical events associated with device separation, feasibility study enrollment was discontinued.

Mitrual annulus diameter at baseline was $36 \pm 3$ mm and at the 3-month follow-up was $35 \pm 1$ mm. No significant trans-mitral gradients were documented at any point during follow-up. Left ventricular ejection fraction at baseline was $42 \pm 11\%$ and at the 3-month follow-up was $50 \pm 6\%$. NYHA failure class at baseline was 2.4±0.5 and at the 3-month follow-up was 2±0.7.

Three of 4 patients in whom the device was implanted had a reduced MR grade at hospital discharge. Baseline MR in the entire group was grade 3.0±0.7 and was reduced to grade 1.6±1.1 at the last postimplantation visit when the device was intact or at the last postprocedural visit in the patient in whom the device was not successfully implanted. MR grade at follow-up as reported by the core echocardiographic laboratory is shown in Figure 4.

The relationship between device shortening, bridge separation, and MR grade is notable, as illustrated in Figure 4. In patient 1, MR was reduced from grade 4 to 0 at 1 month. Device separation with a relatively short 9-mm gap between the proximal anchor and the shortened bridge was documented at 22 days. In patient 3, MR grade was essentially unchanged in the presence of a greater amount (30 mm) of separation documented at 28 days. In patient 5, MR was reduced from grade 3 to 1 at 1 and 2 months, at which time the device remained intact. However, documentation of late bridge separation with a large 41-mm gap at day 81 was associated with the return of grade 3 MR.
Procedural Issues

Coronary venous anatomy is highly variable. A relatively constant feature is the coronary sinus, which opens into the posteromedial right atrium. The major tributary of the coronary sinus is the great cardiac vein, which travels in the left AV groove alongside the circumflex coronary artery. A major tributary is the relatively constant anterior interventricular vein running parallel to the left anterior descending artery in the anterior interventricular sulcus. Together, the coronary sinus, great cardiac vein, and proximal anterior interventricular vein follow the course of the posterior mitral annulus nearly from commissure to commissure.

Three-dimensional angiographic modeling, multidetector-row cardiac-gated CT, and MRI appear promising for the assessment of coronary venous anatomy and dimensions (Figure 5). Visualization of the coronary veins can be accomplished immediately after coronary arterial contrast injections, a technique sometimes helpful during coronary sinus cannulation. Retrograde coronary venography is limited by vigorous backwash resulting from normal venous flow. Consequently, venous opacification is best accomplished with retrograde cannulation of the coronary veins and distal contrast injections. Temporary balloon occlusion of the coronary sinus during venous injections may further improve opacification. Delayed imaging during a coronary CT angiogram also can provide images of a contrast-opacified coronary sinus.

As with coronary arterial imaging, multiple fluoroscopic angulations may be helpful. The left anterior oblique view is helpful in cannulation of the coronary sinus. Cranial angulation may assist cannulation of the anterior interventricular vein, and right anterior oblique angulation may help in appreciation of the course of this vein as it passes along the anterior interventricular sulcus.

Percutaneous Annuloplasty

In the near future, it is unlikely that percutaneous approaches to mitral annuloplasty will reproduce the excellent results of complex surgical repair. However, most surgical repair procedures are not complex, consisting of simple annuloplasty alone. Percutaneous coronary sinus approaches to mitral annuloplasty have been reported to reduce MR in animal models of global left ventricular dysfunction, acute ischemia, and chronic infarction. Several devices (Mitralife Inc, Cardiac Dimensions Inc, and Viacor Inc) have been reported to remodel the mitral annulus and reduce annular anteroposterior diameter in animal models. Pathological examination showed no significant coronary sinus injury, although circumflex artery compression was reported in 1 study. Temporary intraprocedural placement of the C-Cure device in humans confirmed a change in mitral annular shape and mitral insufficiency. To date, there are no published reports of implantation of percutaneous mitral annulus remodeling devices in humans.

Evidence for Effect

It appeared that PTMA was associated with a slight reduction in MR grade immediately after implantation, possibly because of the acute cinching effect of the device. A further reduction in MR grade was observed while the device remained intact, as shown in Figure 4. There was evidence consistent with loss of effect when bridge separation occurred, particularly if a large gap between the bridge segments was observed. Of particular interest was the initial marked reduction in MR documented in patient 5 with recurrence of severe MR after bridge separation. This very limited experience is consistent with, but does not prove, a favorable device effect on functional MR.

Study Limitations

This pilot study was small. Pharmacological management varied throughout the course of the study period. Device failure resulting from separation of the bridge element limits assessment of efficacy. Long-term efficacy and safety remain unknown. Implications for subsequent coronary sinus pacing, retrograde cardioplegia, and mitral valve surgery are unknown.

Conclusions

Percutaneous transvenous implantation of a device in the coronary sinus for the purpose of remodeling the mitral valve annulus is feasible. Initial experience is consistent with a potential beneficial effect on functional MR and warrants further investigation if problems with device separation can be overcome.

Disclosures

Drs Harnek, Kimblad, Munt, Solem, and Webb are consultants to Edwards Lifesciences, Irvine, Calif.
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CLINICAL PERSPECTIVE

Mitral annuloplasty is one of the most common surgical procedures performed for ischemic MR. Animal studies have demonstrated the potential of devices placed in the coronary sinus to remodel the mitral annulus, improve leaflet coaptation, and reduce regurgitation. We evaluated the safety and feasibility of a transvenous catheter-delivered implantable device to provide a percutaneous alternative to surgical mitral annuloplasty in humans. Five patients with chronic ischemic MR underwent percutaneous implantation of an annuloplasty device in the coronary sinus. Initial experience suggests that percutaneous remodeling of the coronary sinus is feasible and may be associated with a possible favorable effect on MR. However, late device failures were associated with clinical deterioration and likely will require device modifications. Percutaneous transvenous mitral annuloplasty warrants further evaluation as a less invasive alternative to surgical annuloplasty.
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