

Percutaneous Mitral Annuloplasty

The status of direct and indirect approaches to treating mitral regurgitation.

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Moderate-to-severe mitral regurgitation (MR) is the most common valvular heart disease in the United States, with a prevalence of approximately 9.5% in patients older than 75 years.¹ In addition, MR is often associated with chronic heart failure. After myocardial infarction (MI), significant MR has been observed in 65% of these patients, with subsequent heart failure within 5 years.² Within this vicious cycle, the presence of MR in patients with heart failure is an independent predictor of mortality.^{3,4} Current guidelines judge the presence of severe MR and symptoms of heart failure, reduced left ventricular (LV) function, enlarged LV diameters, pulmonary hypertension, or atrial fibrillation as an indication for mitral valve intervention, whereby the preferred therapy is mitral valve reconstruction and not mitral valve replacement.^{5,6}

Surgical techniques include methods such as ring implantation, quadrangular resection, leaflet repair, and chordal reconstruction. However, surgical repair comes with all of the risks of open heart surgery. Patients with MR and heart failure frequently exhibit comorbidities, such as chronic obstructive pulmonary disease, renal failure, or diabetes mellitus, and therefore represent a high-risk collective for surgery.^{3,7} Accordingly, the Euro Heart Survey reported that 49% of patients with severe MR did not undergo mitral surgery.⁸ This dilemma is furthermore aggravated by the observation that the 30-day mortality rate for patients older than 80 years was 11% after mitral reconstruction and 18.9% after mitral valve replacement; 90-day mortality was 18.9% after reconstruction and 31.6% after replacement, respectively.⁹ These facts indicate that less-invasive, percutaneous, catheter-based therapeutic interventions are urgently warranted.

The mitral valve apparatus is a complex structure composed of the mitral annulus, mitral leaflets, chordae tendinae, and the papillary muscles. In addition, various pathophysiological mechanisms are involved in the

development of MR. Basically, a differentiation of MR must be made among primary MR, structural MR (ie, prolapse or myxomatous degeneration), and functional MR, resulting secondarily from dilatative or ischemic cardiomyopathy. Because of the pathoanatomical complexity of MR, different approaches of percutaneous catheter-based techniques have been developed.

EDGE-TO-EDGE TECHNIQUE

The edge-to-edge technique was first described by Alfieri et al in the early 1990s.¹⁰ With this technique, a suture from the tip of the anterior to the tip of the posterior mitral valve leaflet was placed, thereby creating a double orifice. The MitraClip device (Abbott Vascular, Santa Clara, CA), positioned through a transseptal access to the region of the mitral leaflets, emulates this approach as a percutaneous technique. To date, more than 3,000 patients have been treated with this technique. Within the randomized EVEREST II (Endovascular Valve Edge-to-Edge Repair Study) trial, mitral clipping was noninferior to surgery, albeit surgery displayed a higher efficacy in regard to reduction of MR, whereas there was improved safety with the MitraClip device. Even after 2 years, both techniques showed significant improvement of clinical symptoms (New York Heart Association classification) and reduction in LV volumes.¹¹ These reductions in LV volumes were indicative of reverse remodeling in patients with end-stage heart failure and severely reduced LV function.¹² Even more interestingly, acute and chronic reductions of the anteroposterior dimensions have been observed, indicating some annuloplasty function of the MitraClip device.¹³

INDIRECT ANNULOPLASTY

The indirect annuloplasty technique is based on the anatomical proximity of the coronary sinus (CS) to the posterior mitral annulus. Insertion of a shortening device in the CS makes this technique comparable with surgical

ring implantation to reduce the mitral annular circumference. Until now, three different systems have been under investigation within clinical trials in humans.

The Monarc system (Edwards Lifesciences, Irvine, CA) consists of three connected components, two self-expanding stents connected with a nitinol bridge. The Monarc device is implanted in the CS via the internal jugular vein (13 F). The distal anchor is first released within the great cardiac vein, and the proximal anchor is then implanted under traction in the region of the CS ostium. The bridge is provided with a biologically degradable coating, which keeps the individual elements of the bridge primarily open. Several weeks after implantation, this coating is resorbed, with subsequent shortening of the system. A total of 83 implantations have been performed so far.

Within the EVOLUTION I (Clinical Evaluation of the Edwards Lifesciences Percutaneous Mitral Annuloplasty System for the Treatment of Mitral Regurgitation) trial, the Monarc device was implanted in 59 of the 72 enrolled patients. The main inclusion requirement was functional MR $\geq$ grade 2+. After 12 months, 50% of these patients who had successful implantation showed a reduction of MR by $\geq$ 1 grade. In patients with severe MR ($\geq$ grade 3+) at baseline, this effect was even more pronounced. Thus, 85.7% of these patients demonstrated a reduction of MR after implantation. The primary safety endpoint (freedom from death, tamponade, or MI after 30 days) was achieved in 91% of patients after 30 days and in 82% after 1 year. Because of the anatomical proximity of the CS to the circumflex coronary artery, 15 patients displayed compression of the circumflex artery that was observed angiographically after implantation of the Monarc system (Figure 1), leading to MI in two of these patients.¹⁴ The follow-up EVOLUTION II study was terminated by the sponsor in June 2010 due to slow inclusion and the complexity of the trial. Subsequently, production of this device has been stopped.

The Viacor percutaneous transvenous mitral annuloplasty (PTMA) system (Viacor, Inc., Wilmington, MA) is also implanted in the CS and comprises a polytetrafluoroethylene catheter (7 F) with three lumens and round nitinol rods. These thin, round bars are inserted in the catheter lumen, causing a ring-shaped structural change and therefore exerting pressure on the mitral annulus to reduce the septolateral diameter and the severity of MR. The PTOLEMY (Percutaneous Reduction of Mitral Valve Regurgitation in Heart Failure Patients) safety and feasibility study included 27 patients with functional MR grade 2+ through 4+, of which 19 patients underwent a diagnostic PTMA procedure. Ultimately, the PTMA device was implanted in nine of these patients. After 3 months, three-dimensional echocardiographic reconstruction indicated a reduction in the septolateral diameters of the mitral annulus by

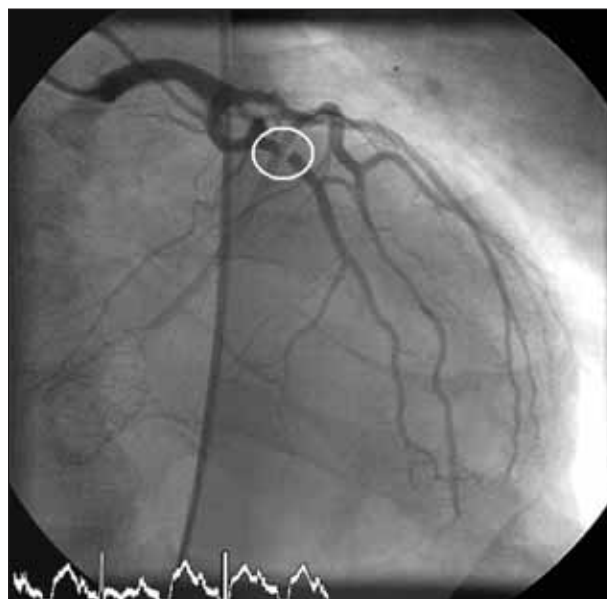


Figure 1. Compression of the obtuse marginal branch in region of the bridge of the Monarc device.

4 ± 1.2 mm.¹⁵ The follow-up PTOLEMY II study included 37 patients with 27 implantations.¹⁶ However, the company ended operations in January, and the study was discontinued in early 2011.

Another CS system is the CE-Marked Carillon mitral contour system (Cardiac Dimensions, Inc., Kirkland, WA). It comprises a self-expanding proximal and distal anchor, connected with a nitinol bridge. Via access through the jugular vein, the system (9 F) is first attached with the distal anchor in the great cardiac vein. Manual pullback on the catheter exerts pressure on the mitral annulus, resulting in improved coaptation of the mitral leaflets. The degree of MR reduction can be controlled by transesophageal echocardiography. Finally, the proximal anchor is released in the region of the CS ostium. An advantage of this system is the possibility of repositioning the device in the event of insufficient MR reduction or the occurrence of coronary artery compression.

The AMADEUS (Carillon Mitral Annuloplasty Device European Union Study) trial indicated the possibility of reducing MR and improving clinical symptoms in patients with heart failure with a major adverse event rate of 13% after 30 days. Overall, the study included 48 patients, and the Carillon device was implanted in 30 of them. After 6 months, five different quantitative echo parameter measurements showed an MR reduction of 22% to 32%. In parallel, an increase in the 6-minute walking distance of 307 ± 87 m at baseline to 403 ± 137 m ($P < .001$) was found after 6 months.¹⁷ These results led to the follow-up study, TITAN (Tighten the Annulus Now). This trial included 65 patients,



Figure 2. Plication with the Mitralign bident system of the mitral annulus at P1 and P3 regions.

with a Carillon device implanted in 36 of those. Within the scope of the study, a clinically inconspicuous fracture of the device was detected by fluoroscopy, which caused a minor change in the device. The rate of major adverse events was 1.9% after 1 month and 25% after 12 months, none of which were device related. After 12 months, a reduction in MR was found in 40% of the patients with the implant, as well as an improvement in clinical symptoms.¹⁸ At the present time, two further studies are planned with the Carillon device. The INTEGRAL study will be a single-center study in South America, and the TITAN II study will be a multicenter study in Europe.

The Mitral Cerclage Annuloplasty system (National Institutes of Health, Rockville, MD) is designed to achieve a circumferential tension in the region of the mitral annulus. A CS guidewire traverses a short segment of the basal septal myocardium that has to be reentered in the right heart where it is exchanged for a suture. Subsequently, tension is applied interactively during imaging and secured with a locking device. Currently, only data from a pig model are available.¹⁹

An advantage of the indirect annuloplasty method is its simple application. However, these techniques have definite limitations. First, the CS is not directly next to the mitral annulus but up to 19 mm above the annulus at the proximal part.²⁰ As a result, the CS devices are possibly less efficacious regarding reduction of MR, and the actual benefit is indirectly the result of compression of the left atrial wall. Second, the anatomical relation of the CS to the coronary arteries is difficult to overcome. An in vivo computer tomo-

graphic examination indicated crossing of the CS over the left circumflex artery in up to 80% of patients.²¹ Cinching in the CS region can therefore cause stenosis or even occlusion of the underlying coronary artery. This may lead to considerable restrictions for the use of these devices within the scope of the indirect annuloplasty studies. Currently, only the Carillon system is still available for use in humans.

DIRECT ANNULOPLASTY

Direct annuloplasty techniques are independent from the CS and are directly applied to the mitral annulus. Different systems with different principles of action, such as retrograde insertion of sutures in the region of the mitral annulus, delivery of ultrasonic energy, or implantation of a ring, are under investigation. Surgical studies have shown that a relatively small plication of the posterior mitral valve annulus (approximately 1 cm) can result in a reduction of the septolateral diameter thereby reducing MR.²² Larger segmental annulus plication (> 2 cm) involves the risk of a systolic anterior motion (ie, the SAM phenomenon) or kinking of the left circumflex artery.²³

The Mitralign system (Mitralign, Inc., Tewksbury, MA) emulates suture segmental annuloplasty. Within the last 2 years, the system was changed from a trident to a bident device. The current Mitralign bident system consists of a set of devices delivering two pairs of surgical pledgets on the P1 and P3 site of the posterior annulus via a retrograde transaortic approach (14-F femoral artery access). The pledgets of each pair are pulled together and locked from the ventricular site of the annulus with a small stainless steel lock (Figure 2), reducing the posterior annulus by approximately 15 mm. The first-in-man (FIM) study is being performed at three hospitals in Germany and one hospital in Brazil. As of this time, the results of 12 patients have been evaluated; five of these patients were treated with the trident system and seven with the current bident system. The changes enabled a significant increase in success of the procedure from 20% to 86% ($P = .028$). After 30 days, one device-related major adverse cardiac event was registered (pericardial effusion). A significant improvement in heart failure regarding the reduction of the New York Heart Association classification from 2.8 at the beginning of the study to 1.9 after 30 days was found in patients with at least one anchor pair ($n = 10$) ($P = .02$).²⁴ Inclusion in this FIM study is currently still open.

With the GDS Accucinch system (Guided Delivery Systems, Inc., Santa Clara, CA), up to 12 anchors are positioned in the region of the mitral annulus via retrograde femoral artery access (14 F). The individual anchors are connected by a cord. Cinching the cord brings the anchors closer together. This cinching within the left ventricle can significantly reduce mitral valve dimensions (septolateral) to

TABLE 1. OVERVIEW OF PERCUTANEOUS MITRAL VALVE ANNULOPLASTY DEVICES AND CURRENT STATUS

Device Name	Company Name	Trial	Technique	Status
Accucinch	Guided Delivery Systems, Inc.	CINCH 2	Direct annuloplasty	FIM
Cardioband Femoral	Valtech Cardio Ltd.	Animal study	Direct annuloplasty	Estimated FIM in 2012
Carillon Mitral Contour	Cardiac Dimensions, Inc.	AMADEUS, TITAN, INTEGRAL, TITAN II	Indirect annuloplasty	Ongoing, CE
enCorTC	MiCardia Corporation	Not available	Direct annuloplasty	In development
MitraClip	Abbott Vascular	EVEREST I, EVEREST II	Edge-to-edge	Clinical, CE
Mitral Cerclage Annuloplasty	National Institutes of Health	Animal study	Indirect annuloplasty	Animal model
Mitralign	Mitralign, Inc.	FIM	Direct annuloplasty	FIM
Monarc	Edwards Lifesciences	EVOLUTION I, EVOLUTION II	Indirect annuloplasty	Suspended
QuantumCor	QuantumCor, Inc.	Animal study	Direct annuloplasty	FIM
ReCor	ReCor Medical, Inc.	SATURN	Direct annuloplasty	FIM
Viacor PTMA	Viacor, Inc.	PTOLEMY, PTOLEMY II	Indirect annuloplasty	Suspended

improve coaptation in ovine hearts. Within the scope of the FIM study, reduced papillary muscle displacement, reduced tenting height, and increased coaptation were directly observed during the procedure. Detailed evaluations are still unpublished up to now. The first percutaneous implantation was performed in September 2009. The CINCH 2 safety and feasibility study is still underway in Germany and Canada.

With the ReCor system (ReCor Medical, Inc., Ronkonkoma, NY), ultrasonic energy is delivered by a balloon catheter (12 F) positioned via a transseptal puncture in the region of the posterior mitral valve annulus. Heating of the collagen causes shrinking and therefore reduction of the annulus and MR. An advantage of this technique is that no implanted foreign objects remain in the patient's body. Within the scope of a canine animal study, an 11% reduction of the mitral annulus could be seen. Histological investigations indicated an increase in elastin coupled with thickening of tissue in the region of the annulus.²⁵ The ongoing SATURN I (Safety and Performance Assessment of Therapeutic Ultrasound for the Treatment of Mitral Regurgitation) FIM study includes seven patients at three centers in Germany.

The QuantumCor system (QuantumCor, Inc., Bothell, WA) is based on the direct delivery of radiofrequency energy at a subablative temperature to the mitral annulus. Currently, the posterior annulus is sequentially treated in four quadrants (from trigone to trigone) to ensure good electrode contact. In a sheep model, an acute reduction of the mean anteroposterior annular distance by a mean value

of 23.8% (anteroposterior diameter reduction 5.75 ± 0.86 mm; $P < .001$) was demonstrated.²⁶ An FIM study with initial application in patients during surgical mitral valve reconstruction or replacement is currently in the planning phase.

The first application of the Cardioband femoral system (Valtech Cardio Ltd., Or Yehuda, Israel) in humans is expected in the second quarter of 2012 within the scope of an FIM study. A type of ribbon, which is fixed with different anchors in the region of the mitral annulus, is inserted via transseptal access to enable direct annuloplasty of the mitral valve. Until now, this system has only been used in a sheep model.

The enCorTC system (MiCardia Corporation, Irvine, CA) is currently still in the developmental phase. It will include a percutaneously implanted, adjustable annuloplasty ring, representing further development of the CE-certified enCor dynamic mitral valve repair system.

The different systems for direct annuloplasty have certain advantages compared with the indirect techniques. However, in general, their application is more complex. At the present time, the Mitralign and Accucinch systems most closely emulate surgical mitral valve reconstruction. Nevertheless, they both require larger arterial access, with possible hemorrhagic and embolic complications. An advantage of the ReCor and QuantumCor systems is that no implants remain in the patient's body. However, all systems currently used in humans have the disadvantage that treatment of the mitral valve comprises only the posterior annulus and not the entire annulus. In this regard, the Cardioband and enCorTC systems could offer some advantages.

TRANSCATHETER MITRAL VALVE IMPLANTATION

There are also several devices in development for transcatheter mitral valve implantation (TMVI). The CardiaQ (CardiaQ Valve Technologies, Inc., Irvine, CA) valve consists of a self-expanding bilevel nitinol frame with porcine pericardial tissue. The effective valve orifice is about 30 mm with a 40-mm anchoring region. The device will be implanted percutaneously via a venous transseptal antegrade approach. Until now, this system has only been used in an animal model. Further bench testing is ongoing. The Cardiovalve (Valtech Cardio Ltd., Or Yehuda, Israel) for percutaneous transfemoral approach is still in development.

Another mitral valve prosthesis is the Endovalve (Micro Interventional Devices, Inc., acquired Endovalve, Inc., Princeton, New Jersey, in April of 2011), which is primarily developed for a minimally invasive surgical approach. Today, in vivo tests in a sheep model were successful. Further tests are ongoing. There is also a percutaneous approach in development. The VXi Vitality (ValveXchange, Inc., Aurora) device is a unique two-part valve system, which will be implanted transapically. This system is still under development.

TMVI may have some advantages, such as providing effective reduction in MR and being less likely to be influenced by variations in morphology. But, there are several challenges, including fixation due to irregular orifice, complexity of subvalvular apparatus, and absence of calcium. Furthermore, avoiding LVOT obstruction and paravalvular leaks is important.

SUMMARY

In general, different devices for treatment of MR are currently under clinical investigation (Table 1). Currently, the MitraClip device has proven to have the highest efficacy and safety in treating either organic or functional MR, yielding to rapidly rising implantation numbers around the world. Indirect annuloplasty devices within the CS displayed only a low efficacy with a rather high rate of adverse events. In addition, due to anatomical considerations of the CS, many patients were found to be unsuitable for device implantation. Thus, CS devices will only play a minor role in the future. With regard to the various direct annuloplasty devices, only scarce data are currently available, precluding any judgment for the future. These techniques are rather complex but have the potential to significantly reduce annular diameter and thereby MR. Nevertheless, due to high morbidity and mortality rates, especially in patients with functional MR, catheter-based techniques will most likely continue to change medicine. ■

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