

Percutaneous and minimally invasive approaches to mitral valve repair for severe mitral regurgitation-new devices and emerging outcomes

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ABSTRACT

Mitral valve disease is common in the United States and around the world, and if left untreated, increases cardiovascular morbidity and mortality. Mitral valve repair is technically more demanding than mitral valve replacement. Mitral valve repair should be considered the first line of treatment for mitral regurgitation in younger patients, mitral valve prolapse, annular dilatation, and with structural damage to the valve. Several minimally invasive percutaneous treatment options for mitral valve repair are available that are not restricted to conventional surgical approaches, and may be better received by patients. A useful classification system of these approaches proposed by Chiam and Ruiz is based on anatomic targets and device action upon the leaflets, annulus, chordae, and left ventricle. Future directions of minimally invasive techniques will include improving the safety profile through patient selection and risk stratification, improvement of current imaging and techniques, and multidisciplinary education.

Key words: Minimally invasive techniques; Mitral valve repair; Morbidity; Mortality; Multidisciplinary education; Risk stratification

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INTRODUCTION

It is estimated that moderate to severe heart valve disease is present in 2.5% of the general population.^[1] Historically, rheumatic heart disease (RHD) was the primary cause of valvular heart disease in adults. The incidence of RHD have declined since the early 1900s; however, it continues to be a significant cause of morbidity and mortality in developing nations.^[2] The prevalence of valvular heart disease is still high around the world, and the most common cause is degenerative changes that are directly related to the increased lifespan of patients.^[3,4] Mitral regurgitation (MR) is the most common valvular heart disease, it affects as many as 9.3% of people ≥ 75 years old.^[1,5] It is estimated that 15–20% of the 5 million people diagnosed with heart failure in the United States have moderate to severe degree of MR.^[6]

Patients with MR that are symptomatic or with a reduced ejection fraction (EF) have

an increased cardiovascular morbidity and mortality.^[7] In patients with asymptomatic MR the optimal time for surgical intervention is poorly defined; however, patients with asymptomatic yet severe MR are at higher risk for cardiac events, including congestive heart failure, new atrial fibrillation and death compared to other patients with less severe MR.^[8,9]

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ETIOLOGY AND CLASSIFICATION OF MITRAL REGURGITATION

In patients with chronic MR, it is critical to distinguish primary (degenerative) from secondary (functional) MR. In primary MR, the pathology lies within the valve components, including leaflets, annulus, chordae tendineae, or papillary muscles. Dysfunction of one or more of these structures causes regurgitation of blood into the left atrium during systole [Figure 1]. The most common causes of MR are rheumatic disease, infective endocarditis, and degenerative disease due to connective tissue disorder such as Marfan's syndrome, Ehlers–Danlos syndrome, Barlow's disease, fibroelastic degeneration, and annular calcification. Papillary muscle rupture from acute myocardial ischemia and infarction is organic ischemic MR and also considered primary MR.^[10,11] In short, “the valve is the disease” and timely correction can restore valve function and improve longevity.^[12,13]

Secondary MR occurs when the mitral leaflets are structurally normal or nearly normal, but the ability of these leaflets to coapt is restricted in globally dilated and hypokinetic left ventricles or with segmental damage that affects valve closure [Figure 2].^[14] It occurs in approximately 20–25% of patients after MI^[15–17] and 50% of those with congestive heart failure.^[18] Dysfunction of the papillary muscles was initially ascribed as the cause of secondary MR.^[19,20] Kaul *et al.*, confirmed that reducing papillary muscle perfusion in isolation produced neither prolapse nor MR, but that MR was related only to the extent and severity of reduction in global left ventricular (LV) function.^[21] Current thought is that the mechanism of secondary MR is multifactorial. Changes in LV geometry, specifically increasing the

sphericity of the LV, can displace the papillary muscles in an outward and/or apical direction restricting leaflet closure in systole.^[22] This is known as leaflet tethering and the posterior leaflet is most often involved.^[23] In hearts with global dysfunction, the annulus of the mitral valve is often dilated^[22,24] and takes on more of a circular shape than its typical “D” shape.^[22,25] Finally, there is often reduced closing force on the leaflets from impaired LV systolic function. Leaflet closure is impaired when lower contraction forces are available to oppose tethering.^[14]

REPAIR VERSUS REPLACEMENT

Mitral valve repair is a technically more demanding procedure than mitral valve replacement (MVR). It consists of reconstruction of the valve and is usually accompanied by mitral annuloplasty. In addition, MR recurs after mitral valve repair in a subset of patients; however, there is growing evidence that preservation of the papillary muscle and its chordal attachments to the mitral annulus is beneficial for ventricular function.^[26,27] Furthermore, the prosthesis itself in case of MVR can thrombose, deteriorate, or increase risk of infection. The number of patients undergoing mitral valve repair is growing, and it has been noted that higher surgical volume would favor better outcome.^[28,29]

Mitral valve repair should be considered the first line of treatment for MR in younger patients, mitral valve prolapse, annular dilatation, and in cases of structural damage to the valve such as chordal rupture or perforated leaflet secondary to infective endocarditis. Older patients with severe rheumatic MR and subvalvular thickening should be considered for MVR.^[27]

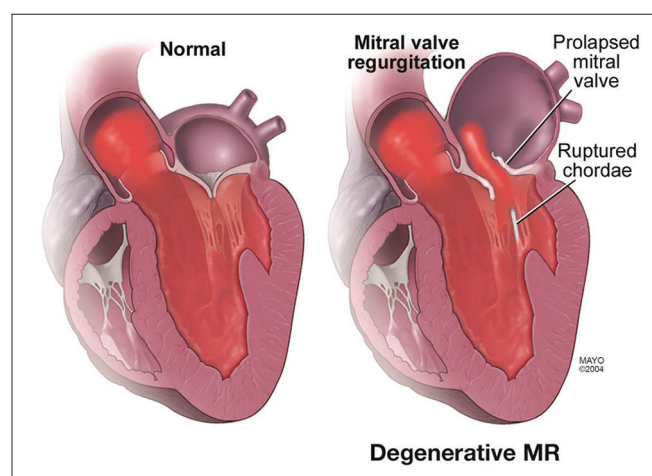


Figure 1: Illustration of normal mitral valve (left) and mitral regurgitation due to ruptured chordae (right)

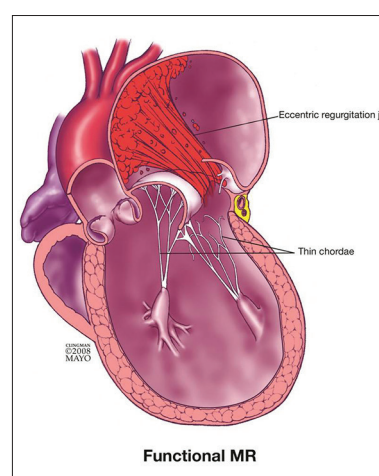


Figure 2: Secondary mitral regurgitation due to annulus dilatation and left ventricular dysfunction

MINIMALLY INVASIVE MITRAL VALVE SURGERY

Several surgical operations fall under the category of minimally invasive mitral valve surgery including robotic mitral valve repair and those performed through lateral thoracotomy. Minimally invasive surgery may be better received by patients and has been shown in the literature that it is not inferior to open sternotomy.^[30] A recent meta-analysis suggests that minimally invasive mitral valve surgery may be associated with decreased blood loss, transfusions, reduced occurrence of atrial fibrillation, reduced length of Intensive Care Unit and hospital stay, reduced time to normal activity,^[31] and reduced healthcare cost.^[32] Several studies that have showed a decreased stroke risk with surgical repair through a sternotomy; however, this could be explained by longer pump time using a minimally invasive approach.^[33-35]

Minimally invasive surgery might be associated with less optimal valve repair, and for that reason it should be preserved for simple repairs, that is, posterior leaflet repair, young patients, and morbidly obese. The referral bias for minimally invasive surgery makes it difficult to compare with open sternotomy. Furthermore, minimally invasive mitral repair requires a skilled surgeon, and the average surgeon now performs 3 per year. For all these reasons, minimally invasive surgery is not yet the standard of care for mitral repair/replacement, but this may change in the coming decade.

PERCUTANEOUS MITRAL VALVE REPAIR

Just as catheter-based techniques have been developed to treat valvular aortic stenosis, percutaneous interventions for MR are evolving. Multidisciplinary approach and collaboration between cardiac imaging and intervention is the key for a successful repair. There are a number of devices under investigation with different approaches aimed to correct the underlying mechanism. A classification system proposed by Chiam and Ruiz^[36] based on anatomic targets and device action include: (1) Leaflets: Percutaneous plication, leaflet coaptation or leaflet ablation; (2) Annulus: Indirect annuloplasty through coronary sinus (CS) or direct annuloplasty including percutaneous and hybrid approaches; (3) Chordae: Percutaneous or transapical chordal insertion or (4) LV: LV remodeling with application of external devices.

The device with the largest clinical experience currently is the MitraClip system [Figure 3] with over 10,000



Figure 3: Representation of the MitraClip – clipping of the A2 and P2 leaflets of the mitral valve creating a double orifice (Image Courtesy Abbott Laboratories)

devices implanted worldwide^[28] (Abbott Laboratories, IL, USA). The repair technique is based on the open surgical leaflet plication reported by Alfieri *et al.* in 1991.^[37] It entails the creation of “double orifice” mitral valve by suturing the free edges of the leaflets at the site of regurgitation together to improve leaflet coaptation and reduce MR. MitraClip uses a percutaneous femoral venous transeptal delivery system to deploy a cobalt chromium clip to secure the mitral leaflets under fluoroscopic and echocardiographic guidance. The device was first evaluated in the Endovascular Valve Edge-to-Edge REpair Study (EVEREST).^[38] In this safety and feasibility study, 107 patients >3+ MR with symptoms, or asymptomatic patients with compromised LV function (EF <60%), regurgitant jet origin of A2 to P2 and a leaflet anatomy amenable to application of the clip underwent the procedure with application of up to 2 clips. Acute procedural success defined as MR \leq 2+ occurred in 79 patients (74%) and at 12 months 66% of nonsurgical patients continued to have MR graded at MR \leq 2+ in severity. In-hospital mortality was <1% with 10 (9.1%) experiencing a major adverse event at 30 days including complications from the transeptal approach, prolonged mechanical ventilation, and bleeding requiring transfusion. At 680 days median follow-up, 75 (70%) of patients remained surgery free.

In 2010, the follow-up EVEREST II^[39] trial was completed which was a randomized controlled trial to evaluate MitraClip treated patients compared to conventional mitral valve surgery with cardiopulmonary bypass in patients with severe MR. Patients were followed for major adverse events at 30 days and clinical success at 1 year. At 30 days, the composite end point of major adverse events (including death, myocardial infarction,

reoperation of the mitral valve, stroke, renal failure, deep wound infection, permanent atrial fibrillation, mechanical ventilation for >48 h, and blood transfusion of >2 units of blood) were compared. The rates of major adverse events were 15% in the percutaneous repair group and 48% in the conventional surgery group. If transfusion was excluded the occurrence of adverse events narrowed to 5% in the MitraClip group and 10% in the conventional surgery group. In terms of durability, at the 1-year mark patients randomized to the MitraClip, 28 (20%) had severe MR and 37 (20%) underwent surgery for mitral valve dysfunction compared with 3 (4%) and 2 (2%) whom underwent reoperation in the conventional surgery group, respectively. There were no reports of device embolization or development of mitral stenosis. MitraClip placement did not exclude the option of surgical mitral valve repair in the future [Table 1].^[29]

The mitral annulus plays an important role in the function of the mitral valve, and its pathologic dilation of the annulus leads to poor leaflet coaptation and MR. Conventionally, the mitral annulus is divided into two components, the anterior fibrous portion and the posterior muscular portion. The anterior portion is thought to be relatively fixed, whereas the posterior portion is in continuity with the atrial and ventricular muscle and affected by dilation of the ventricle. As mentioned previously, functional MR describes cases in which MR occurs as a result of altered function or geometry of the LV or mitral annulus. Most surgical procedures for functional MR are directed at reducing this portion of the annulus by placement of a supporting annuloplasty ring.

There are a number of percutaneous techniques that are under development to treat annular dilation by indirectly “pushing” the posterior annulus anteriorly.^[36]

Indirect annuloplasty techniques exploit the anatomic relationship of the CS and its proximity to the mitral annulus. One such device is the CARILLON® Mitral Contour System (5540 Lake Washington Blvd. NE Kirkland, WA 98033). It consists of self-expandable nitinol proximal and distal anchors connected by a nitinol bridge. The application of tension on the system pulls the posterior mitral annulus anteriorly reducing septal-lateral annular diameter. The AMADEAUS (CARILLION Mitral Annuloplasty Device European Union Study) was a single arm feasibility study to examine the safety and efficacy of the device in patients with secondary MR over 24 months. The patients that received the device demonstrated a reduction in mitral annular diameter and an improvement in MR by at least 1 grade as well as improvement in functional class and quality of life.^[40] The prospective, nonrandomized, multicenter TITAN trial^[41] used a second generation device and included 53 patients with dilated or nonischemic cardiomyopathy with EF <40% and at least moderate (2+) MR. Of these patients, 36 underwent permanent implantation, whereas 17 had the device acutely recaptured for clinical reasons (transient coronary compromise or <1 grade MR reduction) and served as the comparison group. Overall the major adverse event rate for the implanted group at 30 days was 0% with statistically significant improvement in the echocardiographic assessment of MR severity and exercise performance at 12 months. There are a number of limitations to the use of CS reshaping. Surgical anatomy suggests that the CS is 0.5–1 cm away from the mitral annulus^[26] and overlies just over ½ of the total MA perimeter,^[27] other potential limitations include coronary artery compromise due to the close proximity of the circumflex artery to the CS,^[42] slipping of the distal anchor and device fracture.

Direct annuloplasty techniques attempt to more closely reproduce surgical annuloplasty using only

Table 1: Review of percutaneous mitral valve repair trials

Trials	Method	Efficacy	Safety
EVEREST	Single arm study to evaluate the feasibility and safety of mitral clip (n=107)	66% met the composite end-point of improved MR, freedom from cardiac surgery and freedom from death	104 were discharged home 5 patients had bleeding, 3 had atrial septal complications
EVEREST II	279 patients with moderately severe to severe MR (almost half functional) randomized 2:1 percutaneous repair vs. conventional surgery	Effective at reducing MR Lower 30 days mortality Long durability up to 24 months Improved quality of live More frequent additional procedures	Less adverse events and Less blood transfusion in the mitral clip arm
TITAN	The impact of mitral annuloplasty on functional MR in 36 patients	Improvement in 6MWD and Kansas City Cardiomyopathy Questionnaire Improvement in LV geometry	No device related complications reported

MR: Mitral regurgitation, LV: Left ventricular

transvascular approaches. One such approach is derived from a suture only mitral annular plication technique.^[43] The Mitralign System (Mitralign, Inc., Tewksbury, Massachusetts, USA) uses a system of wires and pledgets to plicate the annulus at the P1 and P3 annular locations. The technique uses retrograde transventricular approach to obtain access to the ventricular side of the mitral annulus. Under echocardiographic guidance the tip of the guide catheter is directed to either the P1 or P3 scallop location in the mitral annulus. Once in the appropriate location, a wire is advanced through the annulus using radiofrequency energy. A second wire is then placed using a device specific bident catheter. The bident catheter is a double leg, fork-shaped catheter that tracks and pivots over the first wire to space the second wire either 1.4 or 1.7 cm away. The second wire is advanced through the annulus via the second limb of the bident catheter. Pledgets are placed over both wires, through the annulus with half of the pledget deployed on the atrial side and the other half on the ventricular side. The deployed pledgets are then tied together and the annulus is plicated. The process is then repeated on the other side of the posterior annulus.^[44] In 2014, enrollment was completed in its initial safety and feasibility trial in 61 patients with secondary MR. Results of the trial have not been released but CE approval is being sought in the EU. The Accucinch System (Guided Delivery Systems, Santa Clara, California, USA) is another direct annuloplasty device that is also delivered via a retrograde transventricular approach. A small adjustable cord interlinked with anchors placed along the posterior annulus. The anchors are implanted into the basilar LV beneath the MA. The cord is then tightened and subsequently “cinches” the posterior mitral annulus and basilar myocardium to decrease MR.^[28]

Another system under development is the Valtech CardioBand (Valtech Cardio, Or Yehuda, Israel). This implant more closely resembles a surgical ring and is implanted via the transeptal atrial route. After obtaining transeptal access a steerable catheter is directed to the anterior commissure under fluoroscopic and transthoracic echocardiography (TEE) guidance. The annuloplasty band is placed through the catheter and an anchor is then deployed to secure the band to the annulus at the anterior trigone. The band is then navigated along the posterior annulus towards the posterior commissure with anchors deployed throughout the process.^[45] Once in place, the band is adjusted under TEE guidance to improve coaptation and reduce MR. The device was first implanted

in humans in July 2013 and the CardioBand with Transfemoral Delivery System (Clinical Trials Identifier NCT01841554) (3 Ariel Sharon Ave – Or Yehuda 60376, Israel) is currently recruiting in Europe.

In addition to the therapies mentioned above that affect the leaflets and the annulus, another therapeutic approach is to attempt to restore LV geometry. The iCoapsys device (4020 Gannett Avenue Des Moines, Iowa 50321 USA) consists of 2 epicardial pads connected by a flexible suture like cord bisecting the left ventricle between the papillary muscles. It is placed through a pericardial subxiphoid approach or via a traditional sternotomy if other cardiac procedures are going to be completed such as coronary revascularization, cardiopulmonary bypass is not required. Shortening of the cord reduces LV size in the anteroposterior dimension and improves leaflet coaptation and cord adjustments are done in real-time with TEE guidance. The RESTOR-MV trial randomized patients with coronary artery disease (CAD) and secondary MR to either coronary artery bypass graft (CABG) plus open mitral repair versus CABG plus placement of the Coapsys device (Myocor, Maple Grove, MN). Patients with the Copasys device demonstrated reduce LV chamber size reduced MR and improved survival.^[46-48] Unfortunately, shortly after completion of this trial the company failed financially and the device is no longer available.

Another novel ventricular remodeling device is the Basal Annuloplasty of the Cardia Externally (BACE), (Basal Annuloplasty of the Cardia Externally, Mardil Medical, Inc., Plymouth, Minnesota, USA). The BACE proof of concept prototype consisted of a strip of mesh that was implanted at the base of the heart and positioned at the level of the AV groove and secured with sutures attached to the exterior surface [Figure 4]. In this location, it is designed to stabilize the mitral valve annulus and to reduce the size or prevent further dilation of the basal myocardium. The device was initially studied in 12 heart failure patients with moderate MR and three vessels CAD who underwent CABG and/or LV reconstruction. At the end of the 18 months follow-up, MR remained significantly reduced with a sustained improvement in LVEF and New York Heart Association (NYHA) functional status and no postoperative complications related to the BACE device reported.^[49] A new generation BACE device was created to create less adhesions around the heart should reoperation be necessary, as well as allow adjustability to the band postoperatively. The current device consists of a wide,



Figure 4: Illustration of the Basal Annuloplasty of the Cardia Externally device. The device is implanted around the base of the heart and filled with normal saline through the subcutaneous ports under echo guidance until the mitral regurgitation is improved (Image from Raman J *et al.*, Can we repair the mitral valve from outside the heart? A novel extra-cardiac approach to functional mitral regurgitation. *Heart, lung and circulation*, 2011. 20 (3): p. 157-62. Used with permission)

clear dimethyl silicone band assembly with inflatable silicone chambers. The inflatable fluid chambers are connected by tubing to subcutaneous ports that remain accessible postoperatively for future adjustment if needed.^[50] This device was studied in 5 male patients with secondary MR undergoing CABG. Postprocedure echo showed that MR was reduced to mild or trace in all patients with the device and NYHA functional class has reduced from Class III to Class II in all cases. The VenTouch device (Mardil Medical Inc., Plymouth MN 55441, USA) functions with a similar concept but is deployed from a subcostal incision alone is currently being developed [Figure 5]. Its first-in-human implant was completed early in 2014 with trials ongoing.

In addition to these techniques of valve repair, there are also a number of percutaneous transcatheter MVR devices in preclinical and early clinical evaluation.^[5] Catheter directed MVR via the transeptal or transapical approach offers the potential to provide valve replacement to high-risk surgical patients without a sternotomy, port access or use of cardiopulmonary bypass.^[51] Unlike the traditional transcatheter aortic valve replacement, a suitable prosthesis for the mitral valve may be harder to develop because of the noncircular shape of the mitral apparatus, difficulty anchoring such a device to the anterior portion of the mitral annulus and the potential for displacement of the anterior mitral leaflet into the LV outflow tract.^[22] The feasibility of the approach however has been demonstrated in patients with dysfunctional mitral bioprosthesis^[52] as well as

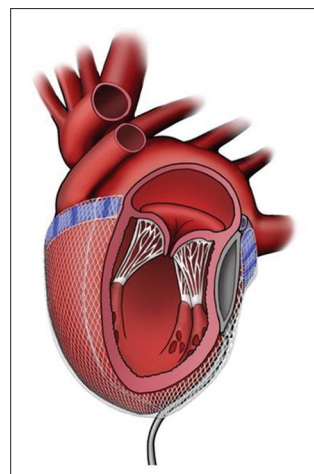


Figure 5: The VenTouch usually slipped around the heart through a small incision the implant provide gentle support to the ventricular wall to minimize mitral regurgitation (Image Courtesy Mardil Medical)

severely calcified native valve mitral stenosis.^[53-55] Acellular three-dimensional (3D) printing of the aortic valve with hydrogel is an evolving and promising technique, the basic principle is to engineer a new valve that mimic the physiological function of the native valve. Given the complex geometry and function of the mitral valve, this technology will require further development before it becomes available clinically.^[40,56]

FUTURE DIRECTIONS

Mitral valve disease is common in the United States and around the world, and patients now have several treatment options that are not restricted to conventional surgical approaches. Early and successful mitral valve repair will lead to improved morbidity and mortality; however, as with traditional surgical approaches, excessively postponing mitral valve repair when utilizing a minimally invasive technique may negatively affect the outcome, or be unable to influence the prognosis. In addition, with more procedural experience, it is becoming increasingly apparent that percutaneous edge-edge repair procedures (such as the MitraClip) may not be applicable for all patients, especially for those with unfavorable mitral valve anatomies such as severe myxomatous degeneration, LV remodeling that has been significant, clefts and calcification in the grasping area as well as commissural pathologies and leaflet anomalies such as inadequate length and asymmetric tethering.^[57] Surgery still remains the first option in patients with severe MR, although percutaneous repair with edge-edge devices such as the MitraClip is rapidly becoming an alternative to surgical MVR in high risk and inoperable patients.

The next decade will bring more data on the safety and long-term durability of these devices. Current outcomes data suggest that early mortality following percutaneous treatment in high-risk groups is not low (9%), in addition >50% of patients are still left with residual >2/4 MR at the end of 1 year postpercutaneous repair.^[57] In order to continue to improve the safety profile of these procedures, forthcoming efforts should focus on the identification of patients most likely to benefit appropriate timing of the intervention, optimization of the procedure and its accompanying devices, and indication and sequencing of complimentary procedures. Future technological advancement in cardiovascular imaging, including 3D echocardiography and fusion imaging, will help guide patient selection and risk stratification, whereas real-time imaging while delivering simultaneous interventions may increase patient safety and reduce procedural time. Finally, education and development of multidisciplinary skill sets, from imaging and surgical technique to peri-operative care, will be essential in this rapidly evolving field.

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Conflicts of interest

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