Transcatheter Mitral Valve Devices – Functional Mechanical Designs

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Abstract

Mitral regurgitation is a complex disorder involving a multitude of components of the mitral apparatus. With the desire for less invasive treatment approaches, transcatheter mitral valve therapies (TMVT) are directed at these components and available at varying stages of development. Therapeutic advancements and the potential to combine technologies may further improve their efficacy and safety. Transcatheter mitral valve replacement, while preserving the mitral apparatus, may emerge as an alternative or even a more suitable treatment option. In addition, early data on transcatheter mitral valve-in-valve and valve-in-ring implantation are encouraging and this approach may be an alternative to reoperation in the high-risk patient. This review details the expanding functional mechanical designs of current active TMVT.

Keywords

Mitral regurgitation, transcatheter mitral valve therapies, transcatheter mitral valve replacement, valve-in-valve, valve-in-ring

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Mitral regurgitation (MR) is a complex disorder requiring the understanding of mitral anatomy and pathophysiology. With the increasing patient population of mitral regurgitation, both functional and degenerative types, and our desire for less invasive treatment approaches, transcatheter mitral valve therapies (TMVT) have emerged. After more than a decade of advancements, development in TMVT still remains in its infancy. Initial therapies were focused on the surgical predicate of repair rather than replacement; now more recent designs on percutaneous mitral valve replacement and access approaches, in particular transapical, are leading advancements in the field. This review is written for the interventionist to understand the intricate mitral anatomy/pathophysiology and the associated functional mechanical designs of current active TMVT.

Mitral Valve Apparatus and Regurgitation

The mitral valve apparatus is a complex structure that requires the integrity of six anatomic components. These components include: the mitral annulus (MA) or left atrioventricular junction, the mitral leaflets, the chordae tendineae, the papillary muscles, the left ventricular myocardium and the posterior left atrial wall.^{1,2} Contraction of the left ventricle (LV) and papillary muscles during systole results in forces that drive the mitral leaflets into apposition. The elevation in LV pressure, compared with left atrial (LA) pressure, allows for coaptation of the free leaflet margins. The MA acts as the fulcrum for the leaflets and is reduced in size during each ventricular systole. Papillary muscle contraction applies the appropriate counterforces to the chordae tendineae, preventing eversion of the leaflets. During normal closure, both leaflets must align in the same plane during coaptation and require an optimal

annular size, a geometrically correct orientation of the papillary muscles, appropriate tethering to the tendinous cords, and suitable closing forces generated by LV muscular contraction.³

For MR to occur, more than one of these components must be dysfunctional. Dysfunctional components to the mitral valve apparatus help to further categorise this disorder and offer many potential options for mechanical correction. This aids in tailoring TMVT according to functional anatomy and device action.^{2,4} Current active TMVT focus on the MA, mitral leaflets, chordae tendineae and papillary muscles. As these technologies improve, so do their applications and the possibilities for combining techniques. When percutaneous mitral valve repair approaches are unlikely to work, transcatheter mitral valve replacement (TMVR) may be a potential option.

Mitral Annulus

The mitral annulus is the D-shaped orifice formed by the convergence of the LA and LV.^{3,5} It is saddle-shaped with elevated septal and lateral segments, and a depressed medial segment along the central zone of apposition.⁶ The anterior mitral leaflet is in fibrous continuity with the aortic valve and the posterior mitral leaflet with the musculature of LV inflow. During systole, the MA contracts reducing the area that the opposing leaflets need to coapt by 20–50 %.⁷ Left ventricular dilatation distends the MA, reducing the ability for the annulus to contract.⁸ In the setting of significant mitral annular calcification, a loss of annular contraction can also lead to leaflet malapposition.⁹

The goal of treating the MA when it is dilated is to decrease the septal-lateral diameter by at least 8 millimetres (mm). Annuloplasty techniques are designed to restore annular size and shape,

subsequently improving leaflet coaptation. Approaches for correction include indirect reshaping or restraining the valvular orifice via the coronary sinus (CS) versus direct via the LA or LV.

Coronary Sinus Indirect Annuloplasty

Indirect annuloplasty utilises the CS to reshape the mitral annulus. The close proximity of the CS to the MA allows for the placement of devices that will shorten the posterior annulus and bring it anteriorly, decreasing the septal-lateral dimension and improving leaflet coaptation. The main difficulty with this technique is that the CS only relates to the posterior annulus and that, in many cases, does not course in the atrioventricular groove along the MA. Furthermore as annular dilatation progresses with worsening MR, the distance from the CS to the mitral annulus increases. Other considerations that would limit the use of these devices include mitral annular calcification that makes it difficult to reshape the MA. In addition, the CS may directly transverse the coronary arteries, most commonly the left circumflex.¹⁰⁻¹² Coronary angiography is necessary to confirm the relationship of the coronary arteries to the CS prior to indirect annuloplasty.

The only available CS device is the CARILLON® Mitral Contour System™ (Cardiac Dimensions Inc., Kirkland, WA, US). It consists of two self-expanding nitinol anchors connected by a fixed-length nitinol intervening cable. After the distal anchor is deployed in the great cardiac vein, the bridge is unsheathed and tension is applied to the cable. Tension can be adjusted to achieve optimal results; subsequently, the proximal anchor is deployed in the anterior interventricular vein. The device is retrievable if results are non-optimal. In the Carillon Mitral Annuloplasty Device European Union Study (AMADEUS) and Tighten the Annulus Now (TITAN) trials, successful device implantation was demonstrated in 62 % of patients with a mean grade reduction of MR by ≥ 1 .^{13,14} This device has CE mark and is awaiting pivotal study in the US.

Mechanical Approach to Direct Annuloplasty

Direct annuloplasty reshapes the MA without use of the CS, preserving native leaflet function and restoring leaflet coaptation. These devices are delivered to the LA or LV and implanted into the MA. The Mitralign device (Mitralign Inc., Tewksbury, MA, US) is delivered retrograde transaortic into the LV periannular space. Two pledgeted anchors are deployed on the posterior mitral annulus at P₁P₂ and P₂P₃ locations, connected by a suture. The pledgets are plicated and secured into place by a stainless steel lock, cinching the posterior MA.¹⁵ First-in-man (FIM) study is ongoing.

The Accucinch Annuloplasty system (Guided Delivery Systems [GDS], Santa Clara, CA, US) utilises a similar technique; however, it has placement of up to 12 retrievable anchors applied from P₁ to P₃, extending from the right to left trigones. A suture connects the anchors with direct tension applied to decrease posterior annular size. Enrolment into Cooling in intracerebral Hemorrhage (CINCH) 2 safety and feasibility trial is underway. Moreover, the Cardioband device (Valtech, Or-Yehuda, Israel) is a sutureless technology where supra-annular fixation is made through an antegrade transseptal approach.¹⁶ Anchors are implanted individually along the posterior annulus and can be repositioned or retrieved, and adjustments made to fine-tune annular dimensions. FIM is also ongoing.

The major limitation of these devices is that they are partial rings that only affect the posterior MA. Currently, placement of a complete

mitral annuloplasty ring is being evaluated in preclinical trials using the Millipede (Millipede LLC, Ann Arbor, MI, US) and enCorTC (Micardia Corporation, Irvine, CA, US) systems. Both are delivered via a transseptal approach and fixed into the periannular space. Unlike its surgical counterpart (enCorSQ device [Micardia Corporation, Irvine, CA, US]) that requires exposure of a subcutaneous atrial lead for radiofrequency activation, the activation of enCorTC is wireless and is adjustable for appropriate MR result by echocardiography.¹²

Mitral Leaflets

The anterior leaflet tends to be the more mobile of the two leaflets, while the posterior leaflet acts as the support structure.¹⁷ The anterior mitral leaflet is in fibrous continuity with the aortic valve, bordered on either side by the right and left fibrous trigones. The areas of both leaflets are identical, with the posterior leaflet being broad (occupying nearly two-thirds of the annular circumference) and short.¹ Leaflet defects typically include excessive/deficient tissue or unrestrained/restricted mobility. The goal of treating the mitral leaflets is to improve leaflet coaptation and to reduce the effective regurgitant orifice area.

Leaflet Plication

Based on the surgical Alfieri technique, percutaneous leaflet plication re-establishes leaflet coaptation by approximating the anterior and posterior leaflets (A₂ and P₂ central segments, site of regurgitation) together via a cobalt-chromium clip.¹⁸ The MitraClip® system (Abbott Vascular, Redwood City, CA, US) creates an effective double-orifice mitral valve, reducing the overall amount of MR for both functional and degenerative types. The system uses a steerable catheter (24F proximally, 22F distally) to deliver the MitraClip transseptally and allow for grasping of the leaflet free edges.¹⁹ The MR jet must be centrally located with sufficient coaptation length of at least 2 mm, a depth from the MA of no more than 11 mm, and if a flail leaflet is present, a gap and flail width not exceeding 10 mm and 15 mm, respectively.

MitraClip implantation is typically guided by conventional fluoroscopy and transoesophageal echocardiography (TOE). The use of live three-dimensional (3D) TOE-fluoroscopy fusion technology (EchoNavigator system [Philips Healthcare, Andover, MA, US]) can potentially further aid in implantation. With this technology, landmarks can be placed at the site of transseptal puncture (3–4 centimetres [cm] above the coaptation plane) and at the central A₂P₂ coaptation or intended coaptation point (if prolapse or a flail leaflet is present) to guide the intervention (see *Figure 1a*). The device can be steered until it is aligned over the landmark and advanced into the LV (see *Figure 1b*). The clip is then retracted for leaflet grasping and device closure. The MitraClip can be repositioned or removed prior to final deployment and multiple clips can be implanted to achieve the desired MR reduction (see *Figure 1c*).

The Endovascular Valve Edge-to-Edge Repair Study (EVEREST) II study enrolled 279 patients with moderate-severe or severe MR in a 2:1 ratio to undergo either MitraClip implantation or conventional mitral valve repair or replacement.²⁰ Successful reduction in MR by at least 1 grade was achieved in 76 % of patients. Composite endpoint of freedom from death, MV surgery or reoperation, and MR >2+ at one year was 72.4 % and 87.8 % (p=0.02), MitraClip and surgery, respectively, in patients with successful in-hospital results. The MitraClip was associated with a significant improvement in New York Heart Association (NYHA) classification with superiority in safety endpoints, major adverse events occurring in 15 versus 48 % at 30 days (p<0.001), compared with

Figure 1: Leaflet Plication Using the MitraClip System and Transoesophageal Echocardiography Fluoroscopy Fusion Imaging

(A) Landmarks were placed using live transoesophageal echocardiography (TOE) fluoroscopy fusion imaging (Philips Healthcare, Andover, MA, US) and overlaid onto fluoroscopy (transseptal puncture: yellow dot/blue arrow and A2P2 coaptation point: red dot). The delivery system can be visualised across the interatrial septum in the left atrium. The first MitraClip device was released at the site of A2P2 coaptation. (B) Repeat imaging revealed significant residual regurgitation medial to the first MitraClip. A second landmark was placed at the site of regurgitation, medial to the first clip, and the delivery system was advanced into the left ventricle as visualised under three-dimensional (3D) TOE. (C) A second MitraClip was positioned and deployed with minimal residual regurgitation.

surgery. Similar results were achieved regardless of the MR type and were maintained at three years. In those requiring surgery, it usually occurred within six months after implantation and surgical options were preserved with 84 % able to undergo successful mitral valve repair.²¹

Leaflet Coaptation

Providing a sealing surface for the leaflets, the Mitra-Spacer™ (Cardiosolutions Inc., Stoughton, MA, US) is a polyurethane-silicone polymer spacer that positions itself at the zone of coaptation, filling the regurgitant orifice. It is anchored to the apex and can be delivered via a transseptal or transapical approach. Pre-sizing balloons are used to appropriately match the spacer to the dimension of the mitral valve (MV) orifice. The device does not alter the MV apparatus and can be fully removed or maintained permanently. Potential complications with the system include thrombus formation or iatrogenic mitral stenosis. The FIM trial resulted in a 1–2 grade reduction in MR without a significant transmitral gradient.²²

Chordae Tendineae/Papillary Muscles

The chordae tendineae originate from the papillary muscles and attach to the mitral leaflets, transmitting ventricular contractions.³ The primary and secondary chordae maintain leaflet apposition and facilitate valve closure, whereas the tertiary chordae help to maintain ventricular geometry.⁵ Abnormalities of the chordae tendineae typically include rupture and presence of abnormally long or short chordae.¹ Papillary dysfunction can occur with fibrosis, ischaemia, or rupture through infarction or trauma. Elongated degenerated papillary muscles can induce prolapse and retracted papillary muscles can make cords vulnerable to disruption.

Chordal Implants/Cinching

Chordal implants are synthetic chords or sutures that can be used to correct leaflet prolapse usually due to ruptured or torn chordae. The implants are attached to the free leaflet margins and anchored to the papillary muscles or LV myocardium. The chords can be delivered either via a transseptal or transapical approach. V-Chordal (Valtech Cardio LTD, Or-Yehuda, Israel), originally designed for an off-pump transatrial approach, allows for chordal implantation with dynamic modulation, able to adjust chordal length under physiological conditions to optimise leaflet coaptation. The device is initially screwed (sutureless) into the papillary muscles; then the chordal length is adjusted by turning a nob; they are subsequently secured to the leaflet margin. FIM trial of seven patients revealed complete procedural

success with 100 % chronic success at two years.²³ The newer transseptal system has a cinching device to secure the chord with two chords allowed for each implant. Preclinical trials are underway.

The NeoChord (NeoChord, Eden Prairie, MN, US) system allows for transapical deployment with fibre optic confirmation of leaflet grasping.²⁴ This device is mentioned due to its off-pump application and potential for percutaneous delivery. Transapical Artificial Chordae Tendineae (TACT) trial enrolled 30 patients with severe MR and isolated posterior leaflet prolapse who underwent placement of at least one artificial NeoChord.²⁵ Acute procedural success was noted in 87 % of patients with 65 % achieving MR reduction to $\leq 2+$ at 30 days. The implantation of multiple chords (2–4 per patient) and fixation to the posterolateral wall translated into higher success rates. All patients requiring subsequent surgery were able to undergo successful repair. NeoChord recently achieved CE mark. Overall, the concern with chordal implants is that aggressive therapy may lead to leaflet restriction and residual MR. Furthermore, the presence of intracardiac material may also predispose the patient to thrombus formation.

Mitral Valve Replacement

Despite the desire to repair rather than to replace the mitral valve, TMVT are currently limited. With the ability to preserve the mitral apparatus, TMVR may be an alternative to repair technologies when suboptimal results are achieved or even a more suitable approach. Unlike the aortic valve and transcatheter aortic valve replacement, the complexities of the mitral apparatus make TMVR a challenge. Concerns for TMVR include the presence of larger annular sizes and asymmetric MA anatomy, the need for appropriate valve anchoring within the MA, and the potential for developing left ventricular outflow tract (LVOT) obstruction and paravalvular regurgitation. Durability issues dealing with stent fracture, tissue erosion and degeneration require evaluation. Multiple TMVR devices that have been developed are in preclinical testing or FIM trials.

The CardiAQ Prosthesis (CardiAQ Valve Technologies Inc., Irvine, CA, US) is a porcine pericardial, trileaflet valve on a nitinol frame that is transseptally delivered.¹³ It has two sets of 12 anchors that secure the device within the MA and preserve the chordae and papillary muscles. It was the first valve to achieve successful FIM in 2012 for severe MR. This patient died on day three due to multisystem organ failure with autopsy not revealing evidence of prosthetic issues. The Cardiovalve® prosthesis (Valtech Cardio Ltd) is also transfemorally delivered

Figure 2: Transcatheter Mitral Valve-in-Valve Implantation

A) Three-dimensional (3D) transoesophageal echocardiography (TOE) revealed severe mitral bioprosthetic valve degeneration with thickened and immobile prosthetic leaflets. (B) TOE QLAB (Phillips Healthcare, Andover, MA, US) analysis confirmed the inner diameter of the bioprosthesis prior to valve-in-valve (ViV) implantation. (C) Using a percutaneous transseptal-transapical approach, a 23 mm Edwards SAPIEN valve (red arrows) was implanted within a 25 mm Carpentier-Edwards bioprosthesis under computed tomography angiography (CTA) fluoroscopy fusion imaging guidance (HeartNavigator, Philips Healthcare, Best, The Netherlands). In yellow, the fused CTA outline of the bioprosthesis can be visualised with a virtual valve in red. Directed transseptal puncture is identified by a blue dot. (D) The same technique was applied for a Melody valve (blue arrows) implanted into a 29 mm St. Jude bioprosthesis, inflated to 24 mm. In yellow, the fused CTA outline of the mitral and aortic bioprosthesis is noted below and above, respectively. The interatrial septum was closed using an Amplatzer Septal Occluder (St. Jude Medical Inc., Minneapolis, MN, US, dark blue arrow).

through a transeptal approach.²⁶ The device has separate fixation and sealing, where the sealing skirt is first implanted followed by the valve. The novel fixation design around both the anterior and posterior leaflets is able to generate >50 N of anchoring force. Preclinical trials are promising and ongoing.

On the other hand, the Tiara prosthesis (Neovasc Inc., Vancouver, BC, Canada) is a trileaflet porcine pericardial valve fixed on a self-expanding frame that is delivered transapically.^{14,15,27} The frame/valvular orifice is D-shaped to mimic the natural shape of the mitral orifice; the flat side of the D is positioned toward the aortic-mitral continuity to prevent interruption with the aortic valve and LVOT. Its atrial lip engages the left atrium and three ventricular anchors secure the valve in place during systole. The ventricular portion of the device has a covered skirt to reduce risk of paravalvular regurgitation. Tiara is repositionable and retrievable, and awaiting FIM later this year. The Lutter prosthesis (Tendyne Medical Inc., Baltimore, MD, US) is a trileaflet bovine pericardial valve fixed on a self-expanding frame.^{27,28} The device, like the Tiara, is delivered transapically and has an atrial fixation system or flat ring that is connected at a 45, 90 or 110 degree angle (three different iterations of the device) to the tubular ventricular portion of the stent. In addition, there is a ventricular fixation system where neochords are attached to the apex to secure the valve in place and a covered skirt to reduce paravalvular regurgitation. Preclinical trials are underway.

Next, the EndoValve™ prosthesis (Micro Interventional Devices Inc.™, Bethlehem, PA, US) is a trileaflet bovine pericardial valve that was

initially delivered transatrially via a right thoracotomy.²⁹ The device is made of a foldable nitinol frame that attaches to the native valve through three anchors or grippers, grasping the native leaflets and MA; a Dacron skirt covers the valve. Recent concern over valve fixation has stimulated valve redesign to create an active fixation system where the device is delivered transapically and anchors are attached to a novel transapical closure device, Permaseal™ (Micro Interventional Devices Inc.). Preclinical trials of the newer generation device are still pending.

Finally, the Ventr Embracer prosthesis (Medtronic Inc., Minneapolis, MN, US) is a trileaflet bovine pericardial valve on a self-expanding nitinol frame.³⁰ The device consists of two components: a large inflow portion that seals to the atrial surface of the MA, and a very short LV projection to avoid subannular and LVOT interference. Support arms engage the A₂P₂ components of the mitral valve, securing the valve in place and creating tension on the atrial portion to improve apposition and reduce paravalvular regurgitation. The device is delivered through a transatrial approach. Preclinical trials are also underway.

Valve-in-Valve/Valve-in-Ring Therapy

Although the TMVR technologies remain in its early clinical stages, current transcatheter valves are being implanted successfully within surgical mitral platforms such as degenerative bioprostheses and complete annuloplasty rings. For patients with degenerative bioprostheses or failed repair, reoperative surgical valve replacement often carries a high mortality risk, especially in older patients with multiple co-morbidities. Transcatheter valve-in-valve (ViV) or valve-in-ring (ViR) implantation is a less invasive option and can be utilised as an alternative to open surgery in the high-risk or inoperable patient.^{31–33}

In the mitral position, the transcatheter valves that are currently utilised 'off-label' are the Edwards Sapien (Edwards Lifesciences, Irvine, CA, US) and the Melody® (Medtronic Inc.) valves. The Edwards Sapien valve is a bovine pericardial valve sutured onto a stainless steel balloon-expandable stent that is Food and Drug Administration (FDA) approved and CE marked for transcatheter aortic valve replacement. The Melody valve is that of a bovine jugular valved vein, which is sutured onto a platinum-iridium stent. It is designed for dysfunctional right ventricular outflow tract conduits. To date, the results of seven Melody ViV implantations within a high-pressure, left-sided haemodynamic environment (one mitral, six aortic) revealed complete freedom from regurgitation and an 86 % freedom from significant stenosis at one-year follow-up.²⁴

The Global ViV Registry with nearly 120 patients included for Sapien mitral ViV and ViR, reported 30 day and one-year mortality rates of 12 % and 25 %, respectively.^{17,34} A majority of implantations, over two-thirds, were performed using a surgical transapical approach. Approximately 5 % had device malpositioning related predominately to the difficulties in achieving coaxial deployment through an antegrade transseptal technique. A newer approach of antegrade transseptal utilising a percutaneous transapical rail provides a complete percutaneous approach to mitral ViV and ViR implantation where creation of the arteriovenous rail has allowed for coaxial deployment and improved fine-tuning of valve positioning within the surgical platform³⁵ (see Figures 2 and 3). Radiopaque fluoroscopic markers of the valve can aid in ViV/ViR positioning. The use of computed tomography angiography (CTA) fluoroscopy (HeartNavigator [Philips Healthcare, Best, The Netherlands]) and TOE-fluoroscopy fusion imaging can

Figure 3: Transcatheter Mitral Valve-in-Ring Implantation

(A) Two-dimensional (2D) transoesophageal echocardiography (TOE) revealed a complete annuloplasty ring with severe para-ring and intra-ring regurgitation by colour doppler. (B) With three-dimensional (3D) TOE, the mitral valve apparatus can be well-visualised. (C) Using a percutaneous transseptal-transapical approach, closure was performed of the mitral para-ring leak using an Amplatzer Vascular Plug II 8 mm and intra-ring regurgitation using a Melody valve-in-ring. In yellow, the fused computed tomography angiography (CTA) outline of the annuloplasty ring can be visualised as well as the aorta and coronary arteries in red.

provide additional landmarks (i.e. sites of transseptal puncture, transapical puncture, mitral bioprosthesis and mitral ring) to perform guided puncture and valve deployment.

Conclusion

Mitral regurgitation is a complex disorder involving a multitude of components of the mitral apparatus. TMVT directed at these components, as described, are available at varying stages of development and able to

treat different pathophysiological substrates. Advancements in therapies and the possibility of combining technologies may further improve their efficacy and safety. TMVR may emerge as an alternative or even a more suitable approach, while preserving the mitral apparatus. Early data on transcatheter mitral ViV and ViR implantation are encouraging, and may be an alternative to reoperation in the high-risk patient. Overall, percutaneous mitral therapies are evolving and options to treat patients with this complicated disorder are expanding. ■

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